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LYE POISONING IN CHILDREN

G. W. KERNODLE, M.D.

GRANT TAYLOR, M.D.
AND
W. C. DAVISON, M.D.
DURHAM, N. C.

CORROSIVE burns of the esophagus, secondary to ingestion of lye, constitute one of the most difficult problems encountered in the pediatric service at Duke Hospital. The availability and the widespread use of this material account for the frequency of poisoning, especially in small children, despite the publicity regarding the dangers of its ingestion. Lye is commonly used by poor people as a cleansing agent, but caustic alkali also is present in washing powders, drainpipe cleaners and paint removers. Some persons do not realize until it is too late that a solution of lye which will "eat the stains from the boiling kettle" will have a much direr effect on the oral or the esophageal mucosa. In the great majority of cases of lye poisoning that we have seen, the blame could be placed directly on the parents who carelessly left a solution of lye in a familiar container within the reach of a thirsty child. Often the child swallows lye because he mistakes the white solution for milk.

TABLE 1.—*Age of Patient at Time of Ingestion of Lye*

Age, Yr.	No. of Patients	Per Cent
0 to 1	3	2
1 to 2	68	50
2 to 5	43	32
5 to 20	13	9
Over 20	9	7
Total	136	100

In regard to the age of the patient at the time of ingestion of lye, table 1 reveals that the majority of lye burns occur in children. Lye poisoning is infrequent under the age of 1 year, the great majority of patients being between 1 and 5 years of age. One may note that 82 per cent of our patients were in this age group.

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital.

Read before the Section on Pediatrics at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 13, 1947.

The ingestion of lye immediately causes painful and difficult swallowing. The lips, tongue and pharynx become edematous, ulcerated and covered with exudate, and, within a few hours, pharyngeal and esophageal edema makes it impossible for the child to swallow his own saliva. The immediate symptoms usually subside in five to seven days, by which time the swallowing of liquid and soft food may have greatly improved. While in the ensuing period there is little difficulty, it should be recognized that this is merely a latent interval and that in most instances, unless treatment is instituted, an esophageal stricture will develop within the following weeks or months.

Immediately after the ingestion of the alkali, an attempt should be made to neutralize the corrosive substance with a weak acid, such as diluted vinegar, lemon juice or orange juice. Removal of the caustic from the stomach by lavage is probably needless because of the neutralization of the alkali by gastric hydrochloric acid, while the resulting trauma may be harmful. Visible burns should be treated with an emollient such as olive oil, and the patient given a sedative to relieve pain. Liquids and soft foods may be given as tolerated. By the fourth day a soft rubber, eyeless catheter filled with mercury or small lead shot should be passed without force into the stomach and allowed to remain in place for two minutes. This procedure should be carried out for every patient, unless the esophagus is seen by direct illumination to be undamaged. In instances in which there is doubt, oral burns from caustic should be considered presumptive evidence of esophageal burns and sufficient indication for early esophageal dilations. The dilations are repeated daily, with a gradual increase in the size of the catheter and the period of dilation, until by the tenth day a no. 30 to 34 French catheter is kept down for five minutes. After daily dilations for two weeks, the number of them is gradually decreased to three a week for two weeks, two a week for one month, one a week for one month, two a month for three months, one a month for six months and two or three a year for several years. If increasing difficulty is encountered during the course of treatment, daily dilations are again performed. Also, fluoroscopic examination with barium sulfate or an esophagoscopic study is advisable if difficulty is encountered. Two previous articles[1] reported that 12 patients were treated by this method at Duke Hospital prior to 1944 and that in none of these did symptoms of esophageal obstruction develop. For 4 children, however, owing to the failure of their families to cooperate, the treatment was not sufficiently prolonged and strictures developed, necessitating a second admission to the hospital for gastrostomy and retrograde dilation.

1. Martin, J. M., and Arean, J. M.: Lye Poisoning and Stricture of the Esophagus, South. M. J. **32**:286-290 (March) 1939. Crowe, J. T.: Poisoning Due to Lye, Am. J. Dis. Child. **68**:9-12 (July) 1944.

Since 1944 we have treated 9 patients according to the method outlined previously, and we have had 1 patient in whom, despite daily dilations, an esophageal stricture developed on the nineteenth day after the ingestion of lye. This patient was a Negro girl 14 years of age who drank a solution of lye with suicidal intent; the result was damage of moderate severity to the esophageal mucosa. In retrospect, we are of the opinion that the no. 24 French catheter used for daily dilations was not large enough to prevent formation of a stricture in this patient, but difficulty was experienced in passing a bougie of larger size. We have observed 5 patients with chemical burns of the mouth secondary to the ingestion of lye for whom no esophageal dilation was advised. The burns of these patients were limited to the lips or to the anterior portion of the oral cavity, and esophagoscopy showed no damage to the esophageal mucosa. A recent follow-up study revealed that no difficulty in swallowing had occurred in any of these patients.

TABLE 2.—*Distribution of Patients Seen*

Type of Patient	No. Seen	Per Cent
Showed definite stricture	97	71
Received early dilations	25	19
Was followed without therapy	5	3
Died during acute phase	1	1
Miscellaneous	8	6
Total	136	100

Unfortunately, at Duke Hospital the majority of the children with burns caused by the ingestion of lye were not seen until esophageal strictures developed. Table 2 reveals the distribution of patients seen. When 8 patients in the miscellaneous group whose records were incomplete or could not be found and the 5 patients who had no evidence of esophageal damage are excluded, it will be noted that only 26 of 123 patients were seen in a sufficiently early stage of esophageal damage so that prophylactic therapy could be instituted. The histories revealed that only 5 of the 97 patients who had esophageal strictures when first seen had had any form of esophageal dilation prior to admission to Duke Hospital. Several of these patients had been admitted to local hospitals for parenteral administration of fluids and sedation during the acute phase, only to be discharged without further therapy when the acute symptoms subsided and the ability to swallow liquids improved. One patient had had a gastrostomy performed for feeding purposes when the parenteral administration of fluids had become difficult. With the improvement of swallowing after the disappearance of esophageal edema, the gastrostomy opening was closed and the patient was discharged without any form of esophageal dilation. In this patient and in the

others who did not receive adequate prophylactic therapy, difficulty in swallowing recurred insidiously, increasing in severity over several weeks as the stricture developed in the burned area. At first, these patients had difficulty in swallowing solid food. Eating became slow, and food was frequently regurgitated; this state was later followed by difficulty in taking liquids. Table 3 reveals the time interval from the ingestion of the lye until the patient was seen with symptoms of obstruction. One may note that more than one half of our patients had sufficient symptoms of obstruction to apply for admission to the hospital by sixty days after the ingestion of lye.

TABLE 3.—*Time Interval from the Ingestion of Lye Until Patient Was Seen with Symptoms of Obstruction*

Time, Mo.	No. of Patients
0 to ½	7
½ to 1	37
1 to 2	20
2 to 3	7
3 to 12	21
Over 12	10
Total	102*

* This total includes 5 patients previously discussed for whom prophylactic therapy was inadequate to prevent formation of a stricture.

TABLE 4.—*Time Interval from Ingestion of Lye Until Only Liquids Could Be Swallowed (After Subsidence of Acute Symptoms)*

Time, Mo.	No. of Patients	Per Cent
0 to 1	19	60
1 to 2	7	22
2 to 3	3	9
3 to 4	1	3
4 to 7	2	6
Total	32	100

For 32 of these patients, the history is revealed that only liquids could be swallowed at the time of admission. Table 4 reveals the time interval from the ingestion of the alkali until all solid foods were regurgitated. It will be noted that without treatment the development of the stricture progresses rapidly, the majority of these patients being unable to swallow solid food thirty days after the ingestion of the alkali. Complete occlusion of the esophagus occurs rarely. Only 1 of our patients had an impermeable stricture.

Since the esophageal opening in children is small, the stricture is more frequently found in the upper third of the esophagus. Table 5 reveals the location of the strictures in our series of 102 patients. Nineteen of these patients had more than one stricture. Children whose

esophageal strictures persist for a long period have numerous systemic and other changes associated with prolonged malnutrition. Bronchitis usually is present due to the spilling of food and secretions into the trachea. It is not the purpose of this paper to discuss the treatment of esophageal stricture but instead to reemphasize the method of avoiding it and the importance of its prevention. For those in whom an esophageal stricture of moderate severity developed because of inadequate therapy, we recommend gastrostomy and retrograde bougienage as outlined by Tucker.[2] Our results with this method of treatment have been satisfactory, although dilations have had to be continued for three to five years in difficult strictures before the patients could be dismissed.

Sixteen of our 102 patients with strictures died during the course of therapy. Secondary causes of the majority of deaths were such conditions as perforation of the esophagus following direct esophagoscopic examination or attempted dilation, mediastinitis, esophagotracheal

TABLE 5.—*Strictures of the Esophagus*

Location	No. of Patients
Upper third	34
Middle third	18
Lower third	17
Upper and middle	6
Upper and lower	6
Middle and lower	7
Undetermined	14
Total	102

fistula or empyema. Our mortality has been greatly reduced since the introduction of such chemotherapeutic agents as penicillin and the sulfonamide compounds. Our only death from lye poisoning since 1943, during which time we have treated 33 patients with the effects of the poisoning, was that of a Negro child who died during the acute phase after the ingestion of a large quantity of lye.

Through the efforts of Dr. Chevalier Jackson, of Philadelphia, legislation was finally passed by Congress in 1927 requiring that caustics be plainly labeled as a poison. This measure was a great step forward in the education of the public concerning the harmful nature of this substance. Caustics must be kept away from children. Carelessness and ignorance of their dangers are too common. A survey by Taylor [3] in 1935 of the effect which legislation concerning lye has had on the incidence of esophageal strictures revealed a 50 per cent decrease in Florida,

2. Tucker, G.: Strictures of the Esophagus: Diagnosis and Treatment, Laryngoscope **41**:426-438 (June) 1931.

3. Taylor, H. M.: A Preliminary Survey on the Effect Which Lye Legislation Has Had on the Incidence of Esophageal Stricture, Ann. Oto., Rhin. & Laryng. **44**:1157-1158 (Dec.) 1935.

Pennsylvania and Arkansas during the year 1934 as compared with the incidence during the year 1926. Therefore, in conclusion, not enough has been done to reduce the incidence of esophageal stricture following the ingestion of lye. A further decrease is possible through the continued education of the public concerning the dangers of this substance and by the early institution of proper therapy. If a child swallows lye, he should be taken to his local physician immediately so that prophylactic dilations of the esophagus can be performed, unless direct vision has demonstrated beyond question that the esophageal mucosa is unharmed.

SUMMARY

One hundred and thirty-six cases of lye poisoning are reviewed. The importance of early dilation in the prevention of esophageal stricture is reemphasized.

Elon College.

ABSTRACT OF DISCUSSION

DR. JOHN AIKMAN, Rochester, N. Y.: Dr. Kernodle, Dr. Taylor and Dr. Davison have performed a great service in again calling attention to the importance of the improved methods of treatment in cases of lye poisoning to prevent stricture of the esophagus.

The use of the Salzer procedure, together with modern methods of esophagoscopy and fluoroscopy, avoids the long, painful and expensive treatment which would otherwise be necessary. Lye poisoning has occurred much less frequently since Dr. Chevalier Jackson called attention to this hazard so forcibly that laws were enacted which required proper labeling of these caustics. In fact, the number of cases seen in Durham is astonishing. It would appear to be a social problem due to poverty, ignorance and carelessness.

Dr. Davison told me that while he was in Baltimore he saw fewer than 20 cases, and I am under the impression that he said he had seen 300 or 400 cases since he had been in Durham. There was but 1 private patient in this group, whom I think he said was insolvent. It is difficult to change housekeeping habits long in existence. If families could afford to purchase commercially made soaps, these accidents with caustics would decrease. One is again impressed with the importance of preventing these and other cases of accidental poisoning in small children. Such tragedies can be reduced by education and by legislation that forces accurate labeling of drugs and poisons. Alkalis and other poisons are constantly being placed on the market for new purposes, under new names, with inadequate information on the package as to the contents and what should be done when accidental poisoning occurs. Manufacturers seem to dislike poison labels. Lists of contents often are vague and are printed in such small type that they are not easily found and read.

Study the subject of accidental poisoning as much as one wishes, and the next accident will be due to some item of which one has never heard. Children are not particular, and toilet-bowl cleaners, drainpipe cleaners, as well as dozens of other articles, cause trouble. If reports of accidental poisoning were required and if the statistics of various hospitals were collected, much useful and astonishing information would be obtained. I again plead that manufacturers be required to place readable and understandable information on the containers of poisonous materials.

I should like to ask Dr. Kernodle for his definition of lye and what alkalis he would place under that heading, and also how his treatment should be modified for accidental acid burns of the esophagus.

I have been informed that the latest figures show an increase in accidental poisoning in the United States among children, another reason that Dr. Kernodle's paper is such a valuable contribution at this time.

Dr. Richard R. O'Toole, Pittsburgh: My colleagues and I do not see the great number of cases of lye poisoning that Dr. Kernodle has indicated. Unfortunately, at the Children's Hospital and at St. Francis Hospital, in Pittsburgh, in the cases we do see the symptoms have progressed to the stage at which we have to resort to gastrostomy and the retrograde form of dilation. I think that as pediatricians we have been somewhat derelict in the general management of the nutrition of these children with the effects of lye poisoning. Certainly, the story of low blood plasma protein levels and low hemoglobin levels in the malnourished child is entirely too common, and it is the same in practically every medical center from which the cases are reported.

We in Pittsburgh think we may have the solution to this problem. We have a convalescent home in Large, Pa., operated in association with the Children's Hospital. Several years ago, we had 3 children in the 2 year age group, which Dr. Kernodle has pointed out to be the most affected. In spite of what we thought of as adequate in the calculation of a diet and in nursing care, the nutrition of these children was not what it should have been. We decided to send them to the convalescent home to see what could be done. Miss Hilton, at Large, devised a unique method of managing these children. She looked over their diets, as we all looked them over, and decided that if the diets in use were inadequate she would provide better ones. She selected 6 robust convalescent 2 year old children and for two weeks observed what they ate. She carefully measured their diet, both qualitatively and quantitatively; she scraped their plates when they were finished eating and weighed and measured that. She arrived at a mean conclusion and devised a method of prorating all the foods the well children had eaten, and here, again, she was quite careful in her preparation. She divided her diet into a schedule of four feedings and fed them through the gastrostomy tube. Of course, she also supplied the necessary vitamins through the tube. The results were gratifying. Not only did these patients improve in their nutrition, but the ordinary psychiatric problems that such children usually have seemed to vanish. In addition to the necessity for the management of their nutrition, I think it should be pointed out that, too often, the mouths, jaws and teeth of these children are neglected. They are not chewing, and their jaws and teeth do not develop. Here, again, we approached this problem satisfactorily by having the children chew on an ordinary hard rubber dental ring, that is, the ring the dentist uses in his procedures. At first, it was painful, as they had not been chewing for a few weeks; but as they continued they were able to manage it well, and their mouth, jaws and teeth developed satisfactorily.

Dr. G. W. Kernodle, Durham, N. C.: In answer to Dr. Aikman's question concerning the number of patients seen, I imagine that any one associated with the pediatric ward at Duke Hospital for the past ten years would estimate that several hundred patients had been admitted during that time for treatment of the effects of lye ingestion. In reviewing the records, however, only 136 cases were found. It was noted that in the majority of these histories, there were several readmissions for various complaints or for retrograde dilations.

Since completing this paper less than two weeks ago, I have seen 3 additional patients. One of these children gave a history of the ingestion of lye one month

previously, with symptoms of obstruction developing two weeks later. The parents stated that during the two weeks preceding the admission to Duke Hospital, the patient had been seen by several physicians, each of whom stated he thought the child's difficulty was secondary to tonsillitis.

I am not familiar with the dictionary definition of lye, but about 100 per cent of our patients swallow what is known as Red Devil Lye. Various cleansing agents contain different percentages of caustic alkali.

In regard to the question concerning the effect of acid on the esophageal mucosa, in my experience it has had more effect on the pyloric region than on the esophageal mucosa. I have had 1 case of pyloric obstruction secondary to the ingestion of concentrated hydrochloric acid. I am fairly certain that a member of the department also reported a case, in which obstruction of the esophagus occurred secondary to ingestion of lactic acid U.S.P. that had been given by mistake in place of cod liver oil.

INFANTILE FORM OF PERNICIOUS (ADDISONIAN) ANEMIA

Report of a Long Term Study of a Case

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BROOKLYN

ACCORDING to the present concept of the pathogenesis of pernicious anemia, the primary change consists in a loss, abiotrophic in nature, of the ability to elaborate sufficient gastric intrinsic factor for normal hematopoiesis. The loss of this function, judged by the clinical course of the disease,[1] occurs in a progressive manner, interrupted by a remarkable tendency to remissions. The latter are of decreasing effectiveness, however, and the final outcome in the case without treatment is fatal. For reasons which are not understood, the disease almost exclusively affects persons who have achlorhydria, and in many cases it has been shown that the gastric anacidity is present for years before the development of anemia.

Lack of antianemia principle in the body resulting from faulty gastric secretion is followed by a train of inflammatory and atrophic changes in the stomach, small intestine and other parts of the alimentary tract, notably the tongue. When the lack of hematopoietic material is not due to primary gastric dysfunction, but is caused, for example, by improper diet or by a disturbance of absorption associated with short circuits in the small intestine, similar inflammatory and atrophic changes occur. In such instances the resulting atrophy of the mucosa of the stomach may, in turn, be responsible for a secondary loss of intrinsic factor in the gastric secretions. Indeed, in the strict sense, such conditions should be regarded as secondary types of pernicious anemia, in contradistinction to the idiopathic disease. They thus serve to focus attention on the fact that secretion of the gastric intrinsic factor is subject to fluctuations and that depression of this function may be brought about in various ways.

In the course of an extended investigation of a case which is about to be described, there arose the possibility of still another type of origin of the defect in the antianemic function of the stomach. Instead of a gradual loss of gastric intrinsic factor through degenerative disease, there might be a congenital absence of this factor, with a resultant infantile

From the Department of Pediatrics, the Jewish Hospital.

1. Hunter, W.: Severest Anemias, London, Macmillan and Company, 1909, p. 147. Cornell, B. S.: Etiology of Pernicious Anemia, Medicine 6:375, 1927.

form of pernicious anemia. The present study is concerned with the evidence for the existence of such a condition. The material was reported in preliminary form in 1935 [2] and has since been amplified through prolonged observation. It deals with the case of an infant girl, the second of 2 siblings to fall ill with what appeared to be the same malady. Her symptoms began at the age of 12 months and slowly progressed to the point where she manifested the usual clinical and laboratory signs of pernicious anemia. Her response to liver therapy and the relapsing character of the illness in the absence of such therapy were closely observed over many years, and the data so accumulated have been analyzed from a number of standpoints.

REPORT OF CASE

History.—M. R., a girl aged 21 months, was admitted to the Jewish Hospital on Jan. 14, 1933, because of increasing weakness, pallor, anorexia and vomiting over a period of several months. She was the third child of Jewish parents who were first cousins. The mother, aged 36, was living and well. The father had recently died of a cerebral tumor, at 40 years of age. The family history was of interest in that the first child, 10½ years of age, was well, but the second child had died at the age of 2½ years, after an illness with a clinical course closely similar to that of the patient. There were no other siblings, and the mother stated that there was no history of tuberculosis or anemia in the parents or in their immediate relatives.

Because of her unfortunate experience with the second child, the mother was careful to note many details in the course of the patient's illness. The infant was born at term, weighed 7 pounds (3,175 Gm.) and appeared normal in all respects. Under the supervision of the family physician, who examined her at frequent intervals, the infant was breast fed for three months, after which she was offered an adequate formula of cow's milk, water and "dextri-maltose" (essentially a mixture of maltose and dextrins). She received a supplement to her diet in the addition of orange juice at 3 months of age, cereals at 4 months, cod liver oil and green vegetables at 5 months and eggs at 6 months, all of which were well taken. Fish never formed a part of the diet. Under this regimen she gained weight and developed normally (fig. 1). She sat up at 6 months, weighed 19 pounds 2 ounces (8,675 Gm.) and was 27 inches (69 cm.) in height at 8 months, stood alone at 12 months and walked at 14 months. She lived in New York city and had never been elsewhere. Except for occasional mild infections of the upper respiratory tract, she was well until the onset of her present illness.

Her illness began insidiously when she was about 12 months of age. At this time it was noted that, although her appetite was good and she appeared well, she frequently vomited all that she had eaten. At a routine examination when she was 15 months of age, she was found to be 30½ inches (77 cm.) in height, with a weight of 21 pounds 8 ounces (9,752 Gm.), a gain of less than 2½ pounds (1,114 Gm.) in seven months. No cause for the vomiting was discovered. From this time it was apparent that the infant's health was failing. She began to

2. Benjamin, B.: Addisonian Pernicious Anemia in Infancy, Am. J. Dis. Child. **50**:1336 (Nov.) 1935.

refuse food; her vomiting became more frequent, and she grew pale, apathetic and irritable. Physical examination at 19 months of age revealed what amounted to total cessation of growth and physical development over a four month period, her weight being 21 pounds 15 ounces (9,951 Gm.) and her height 30½ inches (77 cm). Weakness had become so pronounced that for about two weeks she had been refusing to walk or stand. During the next few weeks—the eighth month of her illness—a loss in weight of 14 ounces (397 Gm.) was noted. She showed little interest in her surroundings, resented being handled and was content to remain alone in a more or less drowsy state for long periods.

When the infant was 21 months old, she was brought to the outpatient department of the hospital at which time admission to the pediatric ward was advised.

Fig. 1.—Photograph of M. R. at 8 months of age, prior to the onset of clinical symptoms.

No history of chewing painted articles could be obtained. Diarrhea was not a prominent symptom, although on a few occasions the stools tended to be loose and somewhat more frequent than normal.

Physical Examination.—The infant was moderately well nourished but was rather small and underdeveloped for her age. She was unable to stand, but there was no conspicuous muscular hypotonicity. Her temperature was 100 F. She appeared listless and chronically ill and was extremely irritable when disturbed. Her weight was 20 pounds 2 ounces (9,129 Gm.) and her height 30½ inches (77 cm.). The circumference of the head was 18 inches (46 cm.); that of the chest, 17¼ inches (44 cm.), and that of the abdomen, 17¼ inches (45 cm.). The skin was lemon yellow and the mucous membranes showed a pronounced pallor.

The face, ordinarily pale, became flushed whenever the child began to cry. There were no petechial or purpuric spots. Her hair was fine and long but exceedingly sparse. The anterior fontanel was closed. The scleras showed a subicteric tint. Normal fundi with absence of hemorrhages were seen on ophthalmoscopic examination. The tongue presented a remarkable appearance. It was pale, thin and atrophic with a glazed surface devoid of papillae. Fissures were not present. There were 13 apparently normal teeth; no hemorrhagic, inflammatory or ulcerative lesions were present in the mouth. Enlargement of the heart was not detectable on percussion, but a soft systolic murmur, best heard at the apex, was audible over the precordium. The abdomen was soft and did not appear enlarged or distended. The edge of the liver could be felt 1 to 2 cm. below the costal margin in the midclavicular line, and the tip of the spleen was just palpable. All the deep reflexes were normal, and the Babinski sign was not elicited.

Laboratory Studies.—Examination of the blood revealed a hemoglobin value of 30 per cent (4.3 Gm. per hundred cubic centimeters),[3] an erythrocyte count of 1,370,000, a color index of 1.1 and a polymorphonuclear leukocyte count of 4,200. With a supravital stain the differential count was 27 per cent mature polymorphonuclear neutrophils, 1 per cent band forms, 1 per cent eosinophils, 67 per cent lymphocytes, 2 per cent monocytes and 2 per cent degenerating cells. Anisocytosis and poikilocytosis of the red cells were present to an extreme degree, and fixed smears showed anisochromia, polychromasia and some stippled forms. There was a predominance of macrocytes, although microcytes were also present in large numbers, the mean corpuscular volume being 96 cubic microns. There were 2 megaloblasts and 2 normoblasts per hundred leukocytes and 2 per cent reticulocytes (1,000 cells counted). Some of the polymorphonuclear leukocytes exhibited characteristic hypersegmentation of the nuclei, visible both with supravital staining and in fixed smears. The platelets in the dried preparations were much reduced in numbers, and several of them were of giant size. The platelet count, made by the method of Dameshek, was 67,000 (that of a normal control was 600,000). The indirect van den Bergh test gave a positive reaction for bilirubin, with a value of 1.75 units; the icteric index was 10.3, and there was increased excretion of urobilinogen, as well as albumin, in the urine. Hemolysis of the red cells in a fragility test began in a 0.42 per cent isotonic solution of sodium chloride and was complete in a 0.32 per cent solution. The bleeding time was eight minutes and the coagulation time five minutes, with normal retraction of the clot. Reactions were negative to tuberculin in doses up to 5.0 mg. injected intradermally, and the Wassermann and Kahn tests gave negative reactions. The stools were normal in appearance, and repeated examinations failed to demonstrate the presence of blood or of ova or parasites. Cultures of the stools were negative for organisms of the typhoid-dysentery group, and a blood culture remained sterile. Analysis of the gastric contents after a test meal showed absence of free hydrochloric acid. Chemical examination of the blood yielded the following values: nonprotein nitrogen, 34 mg., and serum protein, 6.82 Gm. per hundred cubic centimeters; albumin-globulin ratio, 1.32; sugar, 80 mg., and cholesterol, 143 mg., per hundred cubic centimeters. Analysis of the acid-base balance, in terms of milliequivalents, showed total base 143, chlorides 102, bicarbonate 22, proteins 17 and undetermined acids 2. The serum calcium measured 9.7 mg., and the serum

3. The instrument used was a modified Sahli hemoglobinometer with a square tube and solid glass standard, and the readings were repeatedly checked against blood, the oxygen-carrying capacity of which was determined in the Van Slyke apparatus.

phosphorus, 4.4 mg., per hundred cubic centimeters. Roentgenograms of the skull and extremities showed no demonstrable abnormality of the skeletal system.

In view of the hematologic data obtained, it was thought that the case was that of the type described by Cooley and Lee [4] as presenting a "pernicious blood picture in infancy." Various other diagnoses were considered, the chief being that of an atypical form of chronic leukemia. The possibility of pernicious (addisonian) anemia was not seriously entertained because of the general opinion that this malady does not occur in infancy.

Course in the Hospital.—The patient was placed on a regular diet, and therapy was withheld during the preliminary period of observation. An unexplained low grade fever was present, which increased gradually until the temperature reached 104 F. on the seventh day. During this period the weight and the hemoglobin concentration remained stationary, but it was thought that the anemia was too severe to warrant further delay in treatment. Accordingly, the infant was given a transfusion of 150 cc. of whole blood. The anticipated therapeutic response observed in the cases reported by Cooley and Lee failed to occur. Instead, the condition of the patient grew steadily worse. Although the temperature had returned to normal and the hemoglobin was now over 60 per cent, anorexia became so pronounced that progressive loss of weight ensued. Weakness increased to the point where the infant was no longer able to sit up. On the eleventh day in the hospital a slight epistaxis developed. On the fifteenth day the temperature rose abruptly, accompanied this time with clinical and roentgenographic evidence of bronchopneumonia. The infant began to vomit two or three times daily and continued to refuse the greater part of her feedings. On the seventeenth day large numbers of pus cells appeared in the urine. On the eighteenth day a watery diarrhea developed, which lasted five days. It became necessary to treat the condition by greatly reducing the caloric intake and by administering daily hypodermoclyses of isotonic solution of sodium chloride. The pulmonary consolidation underwent resolution in about a week, but the fever persisted, apparently because of the urinary infection. The hemoglobin concentration, in the meantime, dropped to 44 per cent. A second transfusion, of 140 cc. of blood, was given on the twenty-sixth day, after which there was moderate improvement in the infant's condition. There was no recurrence of vomiting or diarrhea, and her anorexia was less pronounced. Fever, with temperatures of 100 to 102 F., however, continued despite the normal appearance of the urine and the lack of evidence of other infection. With her weight stabilized at about 18 pounds 12 ounces (8,505 Gm.), the patient was discharged from the hospital, after seven weeks of observation. The subsequent course of her illness was studied in the outpatient department.

On March 9, three days after leaving the hospital, the patient had moderate epistaxis. This symptom recurred on March 12. She was now in poor condition, almost moribund. Pallor and weakness were striking, and severe anorexia had returned. The possibility that the infant had pernicious anemia was reconsidered at this time, and the decision was made to attempt treatment with the parenteral administration of liver extract. The patient was given a concentrated commercial extract obtained from 200 Gm. of liver on each of two successive days. The response to this form of therapy was dramatic (figs. 2 and 3). Within forty-eight hours after the first injection there was an obvious difference in the appearance of the infant. The anxious look was replaced with a more placid expression. She began to take her feedings with some interest and had already gained 7 ounces

4. Cooley, T. B., and Lee, P.: "Pernicious" Blood Pictures in Infancy, J. Pediat. 1:184, 1932.

(198 Gm.) in weight. The reticulocyte count rose rapidly, reaching a level of 42 per cent on the sixth day. This increase was followed by a steady rise in the erythrocyte and hemoglobin values (fig. 4). Hematologic improvement was accompanied with a remarkable increase in appetite. On the day of the first injection of liver extract the infant could be induced to take only 16 ounces (473 cc.) of unmodified whole milk. Within a week her daily consumption had risen to 28 ounces (828 cc.) of milk, containing 1 ounce (28 Gm.) of cane sugar and 2 egg yolks. This diet was supplemented with an intake of solid food amounting to 10 ounces (283.5 Gm.) of cereal, containing 6 ounces (177 cc.) of milk, 1 tablespoon of scraped beef, 5 ounces (142 Gm.) of mixed vegetable, 1 cup (237 cc.) of junket, ½ banana and a few sweet crackers, the last article being given between the regular feedings because of the constant demand of the infant for something to eat. The daily caloric intake had thus increased within a short period from 320 (38 calories per kilogram of body weight) to 1,425 (148 calories per kilo-

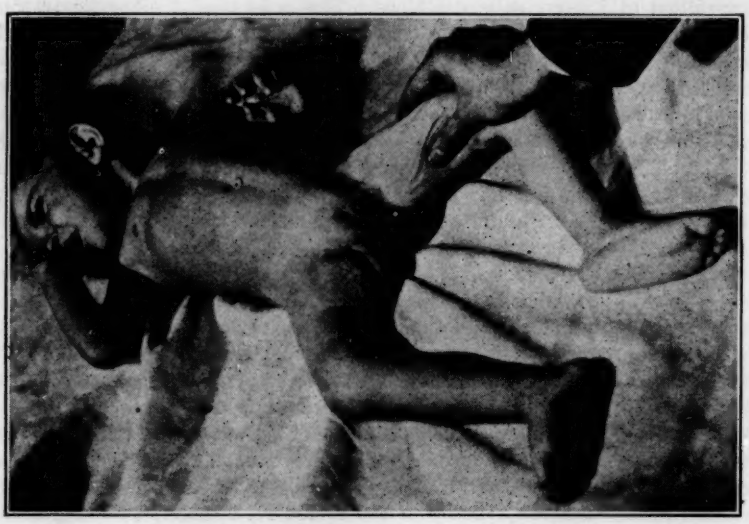

Fig. 2.—Photograph of M. R. forty-eight hours after the first injection of liver extract. Evidence of wasting is apparent. The child was unable to sit up at this time.

gram). This amount was still further increased during the next few days, reaching 1,700 calories by the end of the second week.

Gain in weight and growth during this period were very rapid. Within a month after administration of the liver extract the weight had increased 7 pounds (3,175 Gm.). A few weeks later the curve of her weight passed the level of the average for her age. Similarly, resumption of growth was prompt. After six weeks there was a significant increase in height, from 30½ to 31½ inches (77 to 80 cm.). The curve of the infant's height, however, rose less rapidly than that of her weight, and it was not until about eighteen months later that it attained the level of the normal average (fig. 16). Roentgenograms of the extremities taken three weeks, and again three months, after the institution of therapy showed a dense zone of calcification at the metaphysial ends of the long bones. In the later films this zone had increased in width to 4 mm. and resembled that seen in cases of lead poisoning.

Fig. 3.—Photographs of M. R. at intervals after the first injection of liver extract. *A*, forty-eight hours after first injection, showing the sparse character of the hair growth. The light reflex at the margin of the tongue is caused by the smooth, atrophic surface.

B, six days after the first injection. The child had gained more than 1 pound (454 Gm.) during this interval. The breaking up of the light reflex from the margin of the tongue is due to the beginning of regeneration of the papillae.

C, one month after the first injection. The child had gained 6½ pounds (2,948 Gm.) during this interval. The tongue at this time was normal.

Changes in the tongue following the injection of liver extract were noticeable after one week. Its surface, previously smooth and glossy, became covered with a rough, white coating, and the thin, wasted appearance was no longer present (fig. 3). After a little more than two weeks, the white coating had disappeared, and the tongue was seen to be covered with normal, easily visible papillae.

Progress of the infant in other respects was notably satisfactory. Her disposition changed completely as improvement progressed, and she became happy, playful and full of life. She began to make attempts to walk and within a month was able to do so without support. Two months later she talked intelligibly. At this time her hair began to grow in thickly, and she appeared to be normal in all respects.

On May 15, when the remission induced by liver extract was completely established, analysis of the gastric contents following the subcutaneous injection

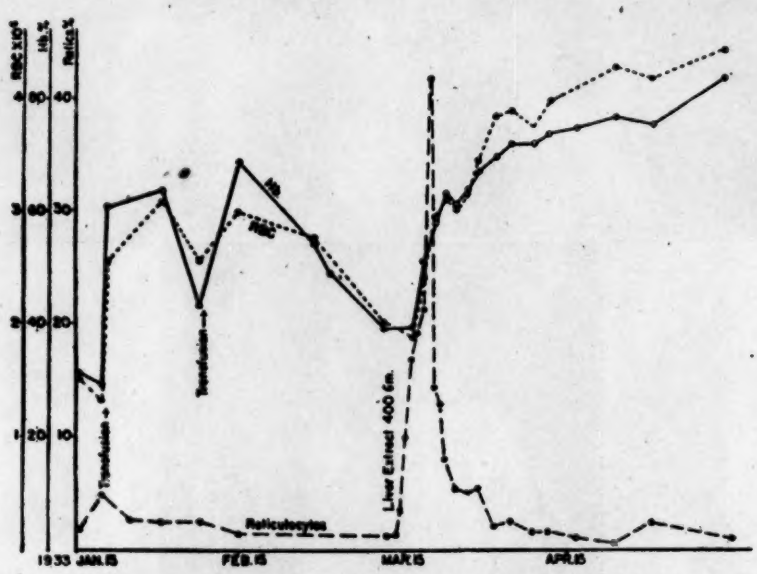

Fig. 4.—Effect on the anemia of blood transfusions compared with that of parenteral administration of liver extract in the initial illness.

of 0.2 mg. of histamine phosphate U. S. P. was made. At this time the level of the patient's hemoglobin was 85 per cent (12.3 Gm. per hundred cubic centimeters), and there were 4,500,000 erythrocytes per cubic millimeter of blood. Continuous extraction for ninety minutes was carried out, with collection of separate samples for each ten or fifteen minute period during the first hour. A total of approximately 25 cc. of gastric juice was obtained. Free acid was absent and the p_H was higher than 7 in all samples.

PLAN OF STUDY

The case which has been described is thus seen to have presented many of the clinical and hematologic features of pernicious anemia as it is encountered in the adult. Since recognition of the malady is hampered by the existence of a number of unrelated diseases which produce

a similar blood picture, considerable diagnostic weight attaches to the hematologic response following administration of liver extract. It is to be recalled that at the time of these observations pediatric experience with the use of liver extract was limited. A few reports, by Faber [5] and others,[6] of favorable responses in infants to the oral administration of liver extract had appeared, but for the most part this material had been used in conjunction with iron in the treatment of hypochromic anemias and as a supportive measure in the treatment of a variety of refractory anemias. The parenteral injection of liver extract in pediatric cases had not been reported. Accordingly, it was difficult to exclude a nonspecific stimulatory effect of the injection or an unanticipated response on the part of the patient to some substance in the extract other than the antianemia principle. The complexity of the problem was increased by the possible presence of one of a number of related conditions, in which the lack in the body of the antipernicious anemia factor may be a result of disorders other than the one to which the term pernicious anemia is applied. There was the added possibility that the illness might be the result of a temporary lack of the antianemia principle. In any event, it was clear that a final diagnosis was not possible at this point and that a prolonged period of further observation was desirable. Moreover, it was held essential for the welfare of the patient that her illness be thoroughly studied, since experience with a similar case was not available in the medical literature.

A plan of study was evolved which would supply the information required for a satisfactory evaluation of the nature of the patient's illness. Since the major points in question related to the specificity of the response to, and the permanence of the need of, liver, it was decided to treat the patient for variable intervals with parenteral or oral administration of whole liver or of extracts of liver and to observe the development of relapses following cessation of therapy. Relapse was considered to have begun when the level of erythrocytes had fallen below 4,000,000 per cubic millimeter and to have become definitely established at a level of 3,000,000 per cubic millimeter. During the period of relapse supplementary observations dealing with either the appearance or the manner of function of the bone marrow, the alimentary tract and

5. Faber, H. K.: Value of Liver Extract (343) in Identifying and in Treating Certain Anemias of Infancy and Childhood: Report of a Case of Probable Primary Anemia in an Infant Nine and One-half Months Old, Am. J. Dis. Child. **36**:1121 (Dec.) 1928.

6. Gerbasi, M., cited by Bachman.[20a] Ducas, P., and Jacquet, J. M.: Deux cas d'anémies graves précoces chez le nourrisson, Arch. de méd. d. enf. **34**:420, 1931. Páez de la Torre, J. M.: Anemia de Biermer observada en tres niños en el curso del año 1932, Semana méd. **2**:1822, 1932.

the central nervous system were carried out. After these observations, various modifications of treatment were instituted, and the ensuing response was noted. In this manner, the course of the child's illness, as well as her growth and development, were carefully followed for a period of fourteen years. The procedure was considered to be a safe one in the absence of evidence of degenerative change in the spinal cord or of other untoward developments that could be detected by frequent examinations. Treatment was never withheld to the point at which the child had to take to her bed. It may be mentioned that success in carrying out the plan of study was made possible only because of the most wholehearted and intelligent cooperation of the patient's mother.

RESULTS

Relapse and Its Relation to Withdrawal of Therapy.—The essential data with respect to the four relapses which the patient was permitted to undergo are summarized in table 1. The manner in which the first three relapses were brought about differed in certain respects from that characterizing the procedure prior to the fourth relapse. The first three relapses occurred during the first two years of treatment, when the principle questions related to proper dosage and to the duration of the effect of a single administration of liver extract. Accordingly, during this period the treatment consisted in a single dose of extract administered in one or two injections,[7] given when the red blood cells had fallen to their lowest levels. The fourth relapse followed a prolonged period of observation of the effectiveness of frequent regular injections of extract in maintaining the child in good health. After two and a half years of this form of treatment, daily oral therapy was instituted for a period of five months. Treatment was thereafter withheld, and the fourth relapse followed. The most pronounced degree of anemia during this relapse occurred twelve and one-half months after cessation of treatment and seven and one-half months after the onset of relapse. Because of severe glossitis at this juncture, as well as anorexia, nausea and diarrhea, 50 Gm. of cooked whole liver was added to the diet daily for twelve days. This addition resulted in amelioration of the patient's symptoms but was insufficient to bring about complete remission. By means of this procedure, which was repeated once again three months later, it was possible without undue risk to maintain the child in a state of relapse for fifteen months.

7. During the period preceding the second relapse, two injections were given, separated by an interval of two and one-half months. The first was a dose of 3 cc., representing the extract obtained from 100 Gm. of liver. This dose proved to be just insufficient to establish a complete remission and was therefore followed by a second injection of 6 cc.

Several points of interest are brought out by the data. It is clear that relapse, i. e., a state of the patient in which the red blood cells were progressively falling below the arbitrarily chosen normal value of 4,000,000 per cubic millimeter, regularly set in when liver extract was withheld. Increasing age during the period of study was without effect in diminishing the tendency to relapse in the absence of treatment. Moreover, withdrawal of therapy had the same effect, regardless of whether the treatment had been adequate for short periods or for an extended period of as long as three years. In each instance relapse followed just as readily; and, as will be described later, the sequence of events, clinical as well as hematologic, adhered to a definite, repeated pattern. The interval during which the red blood cells remained within

TABLE 1.—*Relapses Following Withdrawal of Therapy*

Relapse	Age at Onset *	Previous Therapy	Interval Between Last Treatment and Onset of Relapse, Mo.	Duration of Relapse, Mo.	High Point of Blood Level Following Treatment			Subsequent Low Point of Blood Level During Relapse		
					Hemoglobin		Red Cells/ Cu. Mm.	Hemoglobin		Red Cells/ Cu. Mm.
					Per Cent	Gm.		Per Cent	Gm.	
1	2 yr. 5 mo.	12 cc. extract of 400 Gm. liver by injection	6	5	84	12.2	5,000,000	62	9.0	2,150,000
2	3 yr. 4 mo.	9 cc. extract of 300 Gm. liver by injection	4	1	90	13.1	4,930,000	71	10.3	2,910,000
3	3 yr. 10 mo.	6 cc. extract of 200 Gm. liver by injection	4	2½	90	13.1	4,630,000	54	7.8	2,080,000
4	7 yr. 5 mo.	Powdered extract of 600 Gm. liver daily by mouth †	5	15	88	12.8	5,080,000	59‡	8.6‡	2,180,000‡

* Relapse was considered to have begun when the level of red blood cells had fallen below 4,000,000 per cubic millimeter.

† This form of therapy was given daily for five months immediately after a period of two and one-half years during which normal blood values were maintained by monthly injections of 1 cc. concentrated extract obtained from 100 Gm. of liver.

‡ These values were obtained during the eighth month of the relapse. After this period the patient received inadequate treatment for a short time, and the relapse was permitted to continue seven months longer.

the normal range after a given treatment varied from four to six months. Once relapse set in, the hematologic picture steadily grew worse. Even when the patient was in relapse for many months, there was never any indication of spontaneous remission, at least so far as the blood picture was concerned. It appeared certain that the red blood cells would have continued to decline below 2,000,000 per cubic millimeter had not the practice been adopted of instituting treatment at that point.

One or two additional inferences may be made. That a single injection of liver extract was followed by a period of remission lasting as

long as six months and, similarly, that cessation of treatment after five months of daily oral therapy was followed by a period of continued remission strongly suggest that the active principle was satisfactorily stored in the body. There is some indication also that oral therapy was effective in maintaining the patient in a state of remission, but this point is uncertain because of the possibility of a prolonged carry-over from the previous period of intensive parenteral therapy.[8]

Hematologic Picture During Relapse.—The development of anemia was followed during each of the four relapses, but detailed cytologic studies were confined for the most part to the period of the first relapse. Changes characteristic of typical pernicious anemia as manifested in the formed elements of the blood were observed and are recorded in the following paragraphs.

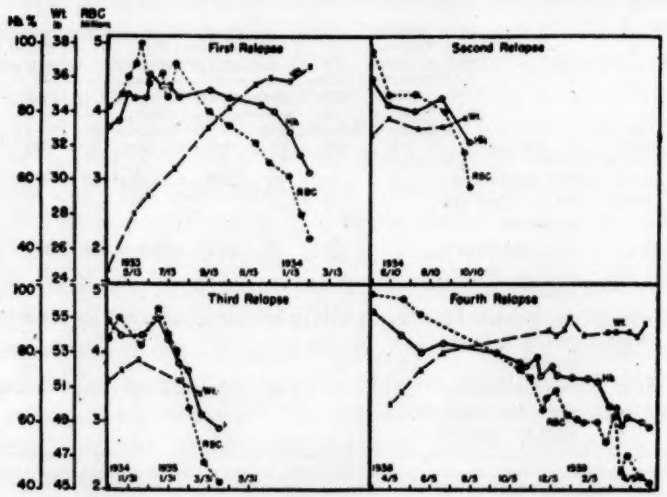

Fig. 5.—Development of hyperchromia of erythrocytes during four relapses. Curves for body weight, indicating that the nutritional state was usually well maintained in spite of the falling blood values, are also shown.

(*a*) Development of Hyperchromia of Red Blood Cells: Curves indicating the increasing color index during each of the relapses are shown in figure 5. It will be noted that a high color index was a constant feature of the exacerbations. Inspection of the curves reveals also that the change in color index began early in the course of the relapse, since the curve for the red cells regularly crossed that for hemoglobin at about the level of 4,000,000 erythrocytes. Once this had occurred, the tendency was for the gap to widen; i. e., the color index tended to

8. The effectiveness of oral therapy was established in subsequent tests.

increase progressively as the red cells decreased. In each instance in which the red cells approached the level of 2,000,000 the color index was approximately 1.4. In the second relapse, which was halted at a less advanced stage, the color index rose to 1.2.

A few determinations of mean corpuscular volume were made, and these are listed in table 2. They serve to corroborate the results of the color index measurements, for they show that when the patient was in remission the value obtained for the mean corpuscular volume of the erythrocytes was the normal one of 81 cubic microns. During relapse the volume increased to 122 cubic microns. The corresponding values for the mean corpuscular hemoglobin content and concentration are also included in the table.

(*b*) Variability of Red Blood Cells: Accompanying the fall in the number of circulating erythrocytes, there occurred an increased vari-

TABLE 2.—*Development of Hyperchromia During Relapse*

Date	Hemoglobin		Red Blood Cells, Cu. Mm.	Volume of Packed Red Blood Cells, per Cent	Mean Corpuscular Hemoglobin Content, Micromicrograms	Mean Corpuscular Hemoglobin Concentration, per Cent	Mean Corpuscular Volume of Red Blood Cells, Cu. Microns	Comment
	Per Cent	Gm.						
1/21/33	30	4.4	1,370,000	13.0	31.4	33.1	96	Initial illness prior to therapy
3/23/33	59	8.6	3,020,000	30.8	27.8	27.1	102	Initial illness 7 days after injection of liver extract
4/25/33	78	11.3	4,350,000	35.2	25.7	31.8	81	Period of remission
1/17/34	76	11.0	2,960,000	34.1	37.2	32.3	115	Period of relapse
2/ 6/34	69	10.0	2,360,000	28.7	42.4	34.8	122	Period of relapse

ability of the red blood cells with respect to size and shape. When the level of these cells reached 3,200,000, definite macrocytosis, as well as increased poikilocytosis and anisocytosis, was apparent on microscopic inspection of blood films. The changes became progressively more pronounced as the severity of the anemia increased. Quantitative evaluation of the variability as expressed in Price-Jones[9] curves was not made, however, during the period of relapse after withdrawal of treatment. The abnormality of the blood was studied by this method during the initial illness one week after the first injection of liver extract and subsequently during a period of completely established remission. For this reason, it is described in another section of the paper.

(*c*) Rate of Decline of Red Blood Cells: Comparison of the behavior of the erythrocyte levels is afforded by plotting the course of the various

9. Price-Jones, C.: Red Blood Cell Diameters, London, Oxford University Press, 1933.

relapses on a single chart (fig. 6). For the sake of clarity, many intermediate points have been omitted, and the curves are constructed of representative points separated, for the most part, by intervals of approximately one month. It will be observed that the decline below the critical level of 4,000,000 seemed to follow two separate paths. The suggestion that the relapses were of two distinct types was subjected to further analysis. Because of the possibility that the speed of relapse might bear a relation to the intensity of the previous period of therapy, a regression line was first constructed to express the decline of the erythrocytes after the longest and most effectively maintained remission (line *1*, fig. *7*). The line, therefore, represents the rate of decline in red cells during the fourth relapse, which followed three years of continuous therapy. All points from the time the erythrocytes fell to 4,000,000 to the time, seven and a half months later, when the relapse

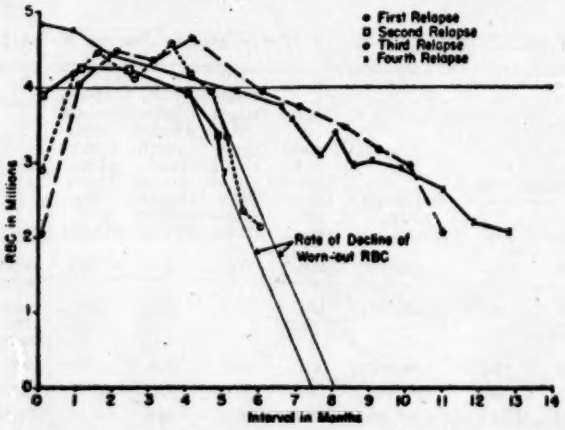

Fig. 6.—Rates of decline of erythrocytes during four relapses, indicating the development of two divergent pathways. Lines (plain) expressing the rate of disintegration of aging red cells of normal persons are included for comparison.

was partially interrupted by treatment have been included. For comparison, a second line (line *2*, fig. *7*) was constructed to express the rate of decline in erythrocyte levels during the second and third relapses, which occurred after the least amount of therapy. The data for these two relapses were combined because their short duration, and rapid development permitted determination of relatively few points. Plotted also on the chart are all the points obtained during the first relapse. Of these, the first five are connected by a broken line, and the remaining points are expressed by a third regression line.

It is apparent that the first and second lines, indicating, respectively, the course of the fourth and those of the second and third relapses, diverge sharply from each other. After the period of most intensive therapy, the rate of fall of erythrocytes was gradual, amounting to

approximately 1,000,000 in four months. On the other hand, minimal therapy was followed by the much more rapid drop of 1,000,000 red cells per month. It is noteworthy that intermediate rates of decline were not observed. Thus, the first relapse, which took place after administration of an intermediate amount of liver extract, did not occur at such a rate as to produce a third straight line falling between lines *1* and *2*. Instead, it was of dual character, at first following closely the line of the fourth relapse and then changing abruptly to follow a course (line *3*, fig. 7) parallel with the line representing the second and third relapses. Similarly, interruption of the relapse by treatment failed to result in a new rate of decline. When minimal oral therapy was instituted during the fourth relapse, it succeeded in temporarily halting the fall of erythrocytes.

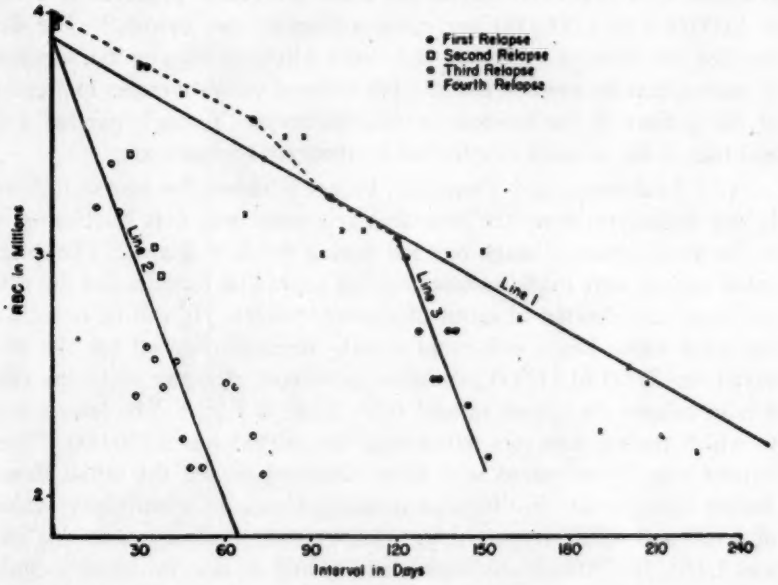

Fig. 7.—Rates of decline of erythrocytes during four relapses. Line *1* expresses the slowest observed rate of relapse (fourth relapse). All erythrocyte counts during the second and third relapses were combined for the construction of line *2*, which expresses the most rapid rate of relapse. The course of the first relapse is represented in part by a broken line and in part by line *3*.

After the effect of the treatment had worn off, however, relapse recurred (fig. 15) at a rate closely expressed by line *1*. It seemed probable, furthermore, that the same phenomenon occurred during the latter part of the initial illness, when the transfusions were given (figs. 4 and 19). Cessation of treatment after the second transfusion was followed by a fall in the red blood cells of 1,000,000 in one month, the rate being that indicated by line *2*.

The following interpretation is offered as a possible explanation of the data contained in these observations: It would appear, first, that

the active principle contained in the liver was well stored in the body. When it was present in excess, the number of erythrocytes was maintained within normal limits. When the stores fell below adequate levels, a fixed, restricted amount of active principle was liberated for hematopoiesis. The amount was such as to result in a gradual fall of the red blood cells. However, when the supply of active principle was presumably exhausted, a rapid decline in the number of erythrocytes ensued. The rate of fall in this instance amounted to 1,000,000 cells per cubic millimeter per month. It is of interest in this connection that transfused red cells are known to persist in the recipient's circulation for from three to four months.[10] In other words, the disappearance of worn-out erythrocytes from the circulation of a child whose normal blood count averages 4,000,000 erythrocytes per cubic millimeter proceeds at a rate of 1,000,000 to 1,300,000 per cubic millimeter per month.[11] The fact that the two rates of decline of red blood cells coincide (fig. 6) suggests, of course, that the periods of rapid fall in blood values were an expression in the patient of the breakdown of erythrocytes through normal wear and tear in the absence of effective erythrocyte regeneration.

(*d*) Leukocytes and Platelets: Figure 8 shows the course followed by the leukocytes from the time that remission was first established up to the most advanced stage reached during the first relapse. The differential counts were made by means of the supravital technic, and the main cell types are charted in terms of absolute values. It will be noted that the total white blood cell count during remission varied for the most part from 7,000 to 11,000 per cubic millimeter, whereas when the child was in relapse the values ranged from 5,300 to 7,200. The lowest level to which the erythrocytes fell during this period was 2,150,000. These figures may be compared with those obtained during the initial illness. Before therapy was instituted, two white blood cell counts gave values of 4,100 and 4,300, respectively. The level of erythrocytes at this time was 1,370,000. After transfusions, and during an interval which included episodes of pulmonary and urinary infection, the leukocytes varied from 4,900 to 6,900.

The most significant factor contributing to the decline of the total leukocyte count is seen to be the fall in the level of the polymorphonuclear neutrophils. If one excludes the count made shortly after a subcutaneous injection of histamine, the counts for the neutrophils during remission show a variation of from 2,500 to 5,300. During relapse, on the other hand, the range was from 1,600 to 2,900 cells. The lowest value for this cell type during the initial illness was 1,100.

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10. Wiener, A. S.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 75.

11. This figure requires little, or no, correction for the increasing blood volume resulting from the slight growth occurring during such a short interval.

Changes in lymphocyte levels during the two periods are not significant. Again, excluding the count after injection of histamine, one notes a range in these cells during remission of from 2,900 to 4,700. During relapse the corresponding values were 2,000 and 4,800. The lowest figure obtained for lymphocytes during the initial illness was also 2,000.

A drop in the level of monocytes, especially in the second half of the relapse, is clearly discernible in the chart. Whereas during remission these cells tended to be at levels of 500 or higher, the development of relapse resulted in their depression to values of 300 or less. Changes in the eosinophils were obscured by the pronounced effect of the injected liver extract, and will be discussed later.

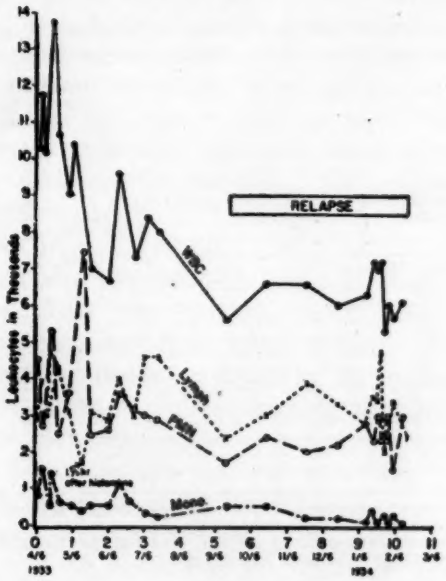

Fig. 8.—Development of leukopenia during the first relapse.

The only qualitative change in the leukocytes which was observed, and which deserves to be mentioned, was the appearance of oversegmentation of polymorphonuclear neutrophils, some of which were unusually large. This change was first noted when the red cells had fallen to 3,560,000 and coincided with the time that the erythrocytes were showing definite macrocytosis.

Only an occasional platelet count during the period of remission and the subsequent first relapse was made. Chief reliance was placed on rough estimates of their numbers in stained blood films. When the erythrocytes were present in normal numbers, the platelets were regularly seen to be numerous and entirely normal in appearance. A platelet

count at this time was 500,000 per cubic millimeter. The platelets continued to be numerous when the erythrocytes had fallen to 3,070,000. When the red blood cells reached 2,150,000, however, the platelets had dropped to 90,000.

(*e*) Bone Marrow: Microscopic examination of sternal marrow obtained by aspiration was carried out during the fourth relapse, when the red blood cells numbered 2,680,000 per cubic millimeter. Although the degree of anemia was thus only moderately advanced, significant changes of the type usually seen in pernicious anemia were recognizable. The results of a differential count of 500 cells are recorded in table 3 and may be compared with those obtained during a subsequent period of remission.

TABLE 3.—*Sternal Marrow During Relapse and Remission*

	Fourth Relapse (May 10, 1939)* per Cent	Fifth Remission (April 6, 1940)† per Cent
Polymorphonuclear neutrophils	17.0	17.4
Band forms	8.0	13.6
Metamyelocytes	9.2	7.0
Neutrophilic myelocytes (all stages with mature granulation)	15.8	13.8
Premyelocytes	5.2	8.0
Myeloblasts	1.2	5.6
Eosinophils	0.4	1.6
Eosinophilic myelocytes	2.2	2.6
Basophilic myelocytes	0.2	0.6
Total myeloid elements	59.2	70.2
Normoblasts	5.0	12.2
Late erythroblasts	4.2	1.6
Early erythroblasts	6.0	0.8
Megaloblasts	10.2	0.4
Total erythroid elements	25.4	15.0
Lymphocytes	13.2	13.2
Mitoses	1.4	0
Megakaryocytes	0	0.4
Unidentified cells	0.8	1.2
Myeloid-erythroid ratio	2.33	4.68

* The hemoglobin concentration was 66 per cent (9.6 Gm. per hundred cubic centimeters); the red cell count, 2,680,000, and the color index, 1.2.

† The hemoglobin concentration was 99 per cent (14.4 Gm. per hundred cubic centimeters); the red cell count, 5,020,000, and the color index, 1.0.

The degree of cellularity of the marrow was not determined by cell count, and estimation of the concentration of cells in several cover slip preparations failed to reveal any clearcut variation from the normal. However, a good indication of increased cellular activity was obtained by measurement of the frequency of cell division. A count of the total number of mitotic figures in an entire cover slip preparation of marrow aspirated during the period of remission showed only 4 cells undergoing mitosis. A similar count revealed 214 mitotic figures in the film of marrow taken during the stage of relapse. By far the greatest proportion of the mitoses during relapse occurred in blastic cells of the erythrocyte series, but a considerable number of neutrophilic myelocytes and 1 eosinophilic myelocyte were seen to be undergoing active division.

The most striking change in the marrow was the appearance of large numbers of megaloblasts. In view of the continued disagreement among American and European hematologists regarding the characteristics of the cell to which this name may be applied, it is advisable to define the various erythroblastic cells as they have been classified in the table. The cell described as a megaloblast (fig. 9 *A* and *B*) was round, or somewhat oval, and approximately two or three times the diameter of a red blood cell. The nucleus was round, often eccentric, and its diameter was usually two-thirds to three-fourths the diameter of the cell. Nucleoli were not seen. The nuclear structure was characteristic, consisting of a uniform, close-meshed, fine chromatin network, usually with little or no evidence of nodal enlargements. The spaces between the chromatin strands were occupied by paler-staining nucleoplasm in such a manner as to give the effect of a fine, even stippling to the nucleus as a whole. The cytoplasm had an appearance of great density, due to the deeply basophilic stain which it took. The stain, however, was not homogeneous but was broken irregularly in many places by small areas of pale cytoplasm, with a color at times suggesting the presence of hemoglobin. The cell resembled in every way the megaloblasts present in the marrow in a typical case of pernicious anemia in the adult (fig. 9 *C* and *D*).

The erythroblasts were divided into two stages, early and late. The early erythroblast (fig. 9 *A*) was smaller than the megaloblast, being about one and one-half times the diameter of a red blood cell, but the proportion of the cell occupied by the nucleus was essentially unchanged. The structure of the nucleus was modified by the increased porosity of the chromatin network and the consequently increased prominence of the nucleoplasm. At the same time, nodal enlargements had made their appearance, and the differentiation of chromatin and nucleoplasm was distinctly sharper than in the megaloblast. The result was to give the stippling of the nucleus a more clearly defined and somewhat coarser texture than that seen in the megaloblast. Changes in the cytoplasm had usually advanced to the stage at which the deeply basophilic cytoplasm was replaced with a paler blue, less dense cytoplasm showing definite beginning hemoglobinization.

The late erythroblast (fig. 9 *A*) was typical of the cell seen, for example, in the peripheral blood in cases of erythroblastosis fetalis. The cell, and particularly the nucleus, were considerably smaller than the early erythroblast. The characteristic nuclear architecture, with its large nodal masses of chromatin, was present and the cytoplasm usually showed a muddy, polychromatophilic stain. The normoblast (fig. 9 *C*) was the generally recognized type, with pyknotic or dense "wheel spoke," nucleus and more or less complete hemoglobinization of the cytoplasm.

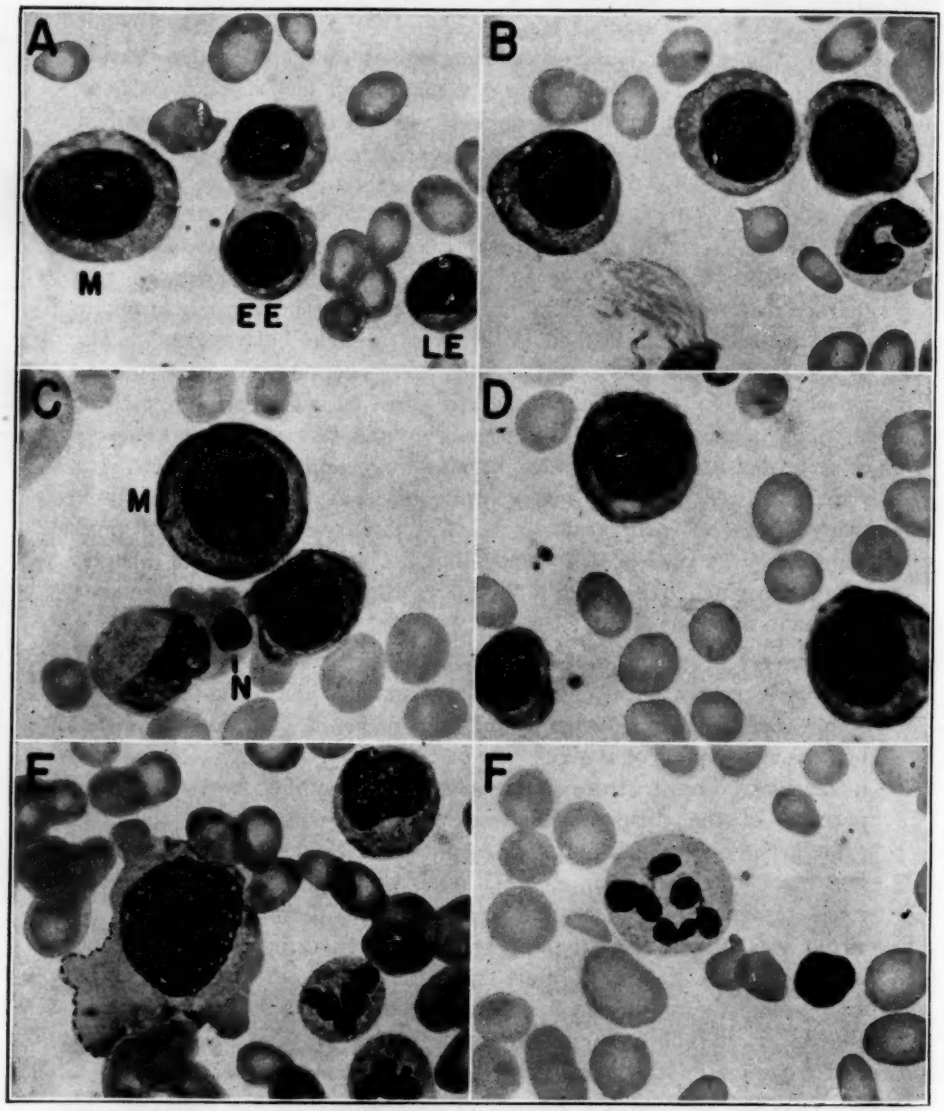

Fig. 9.—Photomicrographs of bone marrow cells during relapse. Typical megaloblasts from the sternal marrow of the patient (*A* and *B*) may be compared with corresponding cells from an adult with pernicious anemia (*C* and *D*). In *F* a hypersegmented polymorphonuclear leukocyte from the patient's marrow is shown. The large size of the cell is evident in comparison with the two mature cells and the myelocyte in *E*. The letter *M* indicates a megaloblast; *E E*, an early erythroblast; *L E*, a late erythroblast and *N*, a normoblast. May-Grünwald-Giemsa stain; × 980.

Reference to table 3 discloses several significant changes shown by the erythroid elements during relapse. First, the total percentage of these cells was 25.4, as compared with the value of 15 per cent during remission. This increase, together with a somewhat decreased number of myeloid elements, resulted in a myeloid-erythroid ratio during relapse of 2.33, almost exactly one-half the value of 4.68 for the period of remission. It will be noted also that the increase in erythroid elements was accompanied with a clear shift to the left, i. e., in the direction of immaturity, of the component cell types. Thus, almost two-thirds of the cells during relapse were megaloblasts and early erythroblasts. This proportion may be compared (fig. 10) with that for the period of remission, when the normoblasts and late erythroblasts constituted over 90 per cent of the erythroid cells of the marrow.

Additional deviations from the normal during the relapse were observed among other cell elements. Many examples of hypersegmentation of polymorphonuclear neutrophils were noted (fig. 9*F*). Some of these cells showed as many as seven distinct segments to the nucleus. The platelets and, finally, the megakaryocytes were greatly reduced in number. Since the figures in the table do not adequately reveal the change affecting the megakaryocytes, counts of the total number of megakaryocytes in entire cover slip preparations were carried out. In comparable marrow films, 5 megakaryocytes were noted in the smear obtained during relapse, whereas the count was 42 for the period of remission.

Clinical Features of Relapse.—The development of clinical symptoms and signs and their relation to the hematologic relapse are of considerable interest and will therefore be described in detail. The symptoms may be divided into those which reflected the constitutional effects of the disease and those referable to disturbances of the alimentary tract. In the former group are included the apathy, listlessness, anorexia, weakness and general slowing of motor activity. Glossitis, vomiting, constipation and diarrhea comprise the latter group.

Most striking, at least during the more gradual relapses, was the fact that the anemia was well advanced before any symptoms became apparent. This slow appearance of symptoms was illustrated by the first relapse, which was observed for a period of five months before it was terminated by treatment. Relapse was considered to have begun Sept. 14, 1933, at which time the erythrocytes numbered 3,980,000 per cubic millimeter. A progressive fall of the red blood cells occurred (fig. 5), so that on December 19 the count was 3,240,000. During this period of three months no abnormal symptoms whatever were detected. The child was alert and active; her appetite continued to be excellent, and her bowel function remained normal. Development of pallor was questionable. The interval was marked also by a gain

in weight of over 3 pounds (1,361 Gm.) and an increase in body length of a little more than 1½ inches (3.8 cm.).

The first unusual symptom was a period of constipation, beginning December 28 and lasting four days. At this time the erythrocytes had fallen to 3,070,000 per cubic millimeter. This period was followed by a return to normal regularity of bowel movements during the next eight days and was succeeded by a period of diarrhea of ten days. The

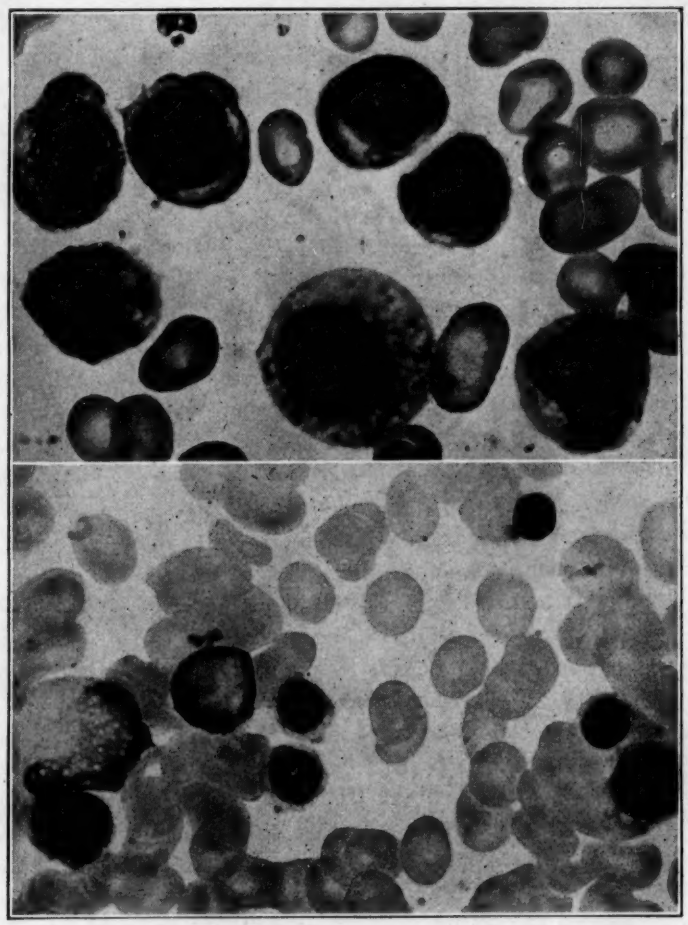

Fig. 10.—Photomicrographs of bone marrow cells before and after treatment of relapse. The transformation from a megaloblastic (upper) to a normoblastic marrow (lower) is clearly evident. May-Grünwald-Giemsa stain; × 1,180.

stools numbered three daily, were large and semiformed and had a foul odor. There followed a short interval of constipation, and a subsequent resumption of normal bowel function. Preceding the onset of diarrhea by several days were a number of new symptoms. Chief of these was

vomiting, which occurred repeatedly, especially in the evening. At the same time there was a sharp diminution in the child's appetite. Details regarding the intake of food are listed in table 4, where it will be noted that the child's weight was well maintained even during the period of acute symptoms. It may be observed, also, that the patient continued to take the essentials of a good diet throughout her illness. The only food which was completely refused during the final month of the relapse was meat. The other foods which were not eaten, namely, bread and desserts, were eliminated because the more important articles of her diet were taken poorly.

The development of redness and inflammation of the tongue coincided with the sudden loss of appetite previously described. Examination revealed typical glossitis confined to a small area near the margin on the right side. The papillae in this region were extremely swollen, but there was no ulceration and the rest of the mouth seemed normal. At first the child did not appear to have any local discomfort, but the aggravation of the process in the succeeding weeks brought forth complaints of soreness of the mouth in eating. The glossitis became more extensive, finally involving the margin of the dorsal surface of the tongue in a continuous rim from the region of the first molar on the right side to that on the left. Extension of the inflammatory process occurred in an irregular manner, alternating with periods of improvement. In most of the affected areas the redness eventually subsided completely and was followed by an atrophic change, characterized by partial or total disappearance of the previously hypertrophied papillae. When the relapse was terminated, only a tiny area of active glossitis remained on the left side of the tongue. The central portion of the tongue, which had never been involved in the inflammatory process, continued to have normal papillae.

Apathy, listlessness and weakness became pronounced during the last few weeks of the relapse. The child lost interest in her surroundings, and increasing weakness necessitated her being carried to and from the subway on her visits to the hospital. A curious slowing of all movements, a change which became even more apparent in subsequent relapses, developed at this time. Even the simplest acts in the daily routine were unduly dragged out.

One of the last signs to be observed was increasing pallor. The delay in its appearance is perhaps not surprising, since the level of hemoglobin did not fall to the same extent as did the erythrocytes. Although slight enlargement of the spleen occurred in later relapses, it was not noted during the first relapse. Evidence of a tendency toward bleeding, likewise, was absent during the first relapse, but mild epistaxis occurred a few times in the subsequent exacerbations of her illness.

TABLE 4.—*Daily Food Intake in Relation to First Relapse*

Date	June 5, 1933	Dec. 19, 1933	Jan. 12, 1934	Jan. 20, 1934	Jan. 30, 1934	Feb. 3, 1934	Feb. 19, 1934	Feb. 21, 1934
Red blood cells per cu. mm.	5,090,000	3,240,000	3,070,000	2,680,000	2,680,000	2,680,000	3,230,000	3,470,000
Comment	Remission	Relapse; period prior to clinical symptoms	Constipation, followed by glossitis and diarrhea	Symptomatic improvement; normal stools	Anorexia; vomiting; sore tongue	Apathy	Six days after injection of 3 cc. concentrated liver extract	Marked clinical improvement
Body weight, Kg.	13.2	16.4	16.3	16.6	16.7	16.5	16.8	16.8
Diet (average per day from June 5 to Dec. 19, 1933)								
Milk	36 oz.		24 oz.	32 oz.	24 oz.	20 oz.	28 oz.	31 oz.
Cooked cereal	8 oz.		4 oz.	6 oz.	4 oz.	4 oz.	8 oz.	9 oz.
Mixed vegetables	4 oz.		2 oz.	3½ oz.	3 oz.	2 oz.	4 oz.	5 oz.
Scraped beef	½ oz.		....	.....	.....	.....	1 oz.	1 oz.
Eggs	2		2	2	2	2	2	2
Dessert	4 oz.		....	.....	.....	.....	1½ oz.	2 oz.
Bread	1 slice		....	.....	.....	.....	.....	1 slice
Orange juice	3 oz.		3 oz.	3 oz.	3 oz.	3 oz.	3 oz.	3 oz.
Cod liver oil	3 tsp.		3 tsp.	3 tsp.	3 tsp.	3 tsp.	3 tsp.	3 tsp.
Miscellaneous items	....		....	3 sweet crackers	.....	1 prune	3 sweet crackers	5-6 sweet crackers
Approximately total daily calories	1,270		840	1,150	840	800	1,160	1,390
Calories per Kg. of body weight per day	86*		52	69	50	48	69	83

* Average value.

Brief mention may be made regarding variations in the clinical picture in later relapses. Although the second and third relapses followed a comparatively short, acute course, the general sequence of events was essentially similar to that already described. However, the onset of symptoms occurred considerably earlier and coincided much more closely with the beginning of hematologic evidence of relapse. The third relapse, unlike the others, was ushered in with a period of severe constipation, accompanied with glossitis, at a time that the erythrocytes numbered 4,230,000 per cubic millimeter. Two weeks later, when the count had fallen to 3,970,000, the bowel function was normal, but anorexia and glossitis were present.

Glossitis was an especially prominent and persistent symptom during the fourth relapse. It appeared seven months after cessation of oral liver therapy and was more or less constantly in evidence during the next thirteen months of the period of relapse. The onset of glossitis coincided with the development of hyperchromia, the level of the erythrocytes being 3,170,000 per cubic millimeter and the color index 1.2 (fig. 5). The inflammatory changes were not always confined to the papillae at the margins of the tongue but occasionally extended to involve the under surface of the tongue and the floor of the mouth, especially in the region of the sublingual ducts. The soreness of the mouth at times interfered seriously with eating. Fortunately, this troublesome feature occurred only infrequently.

When the glossitis was severe, it was usually accompanied with other evidences of disturbed gastrointestinal function. Vomiting was the commonest symptom, and on a number of occasions there was moderate diarrhea. During several of these episodes the child was seized with severe abdominal pain, diffuse in character and without localizing tenderness or muscular spasm. The association of one of these attacks with a particularly severe exacerbation of the glossitis was noteworthy. At this time, the under surface of the tongue was intensely reddened, and the accompanying edema was so pronounced as to impart a gelatinous appearance to the lingual tissues.

Examinations were made repeatedly during periods of relapse, as well as remission, for signs of degenerative changes in the spinal cord. Tests for vibratory sensation and for sense of position were included in the neurologic examinations, and the patient was questioned with regard to paresthesias. At no time did any evidence appear suggesting involvement of the central nervous system.

Gastric Function During Relapse.—Studies were carried out to determine the ability of the stomach to secrete acid, and tests were made for the presence or absence of the intrinsic factor of Castle.

Tests for gastric acidity were made during the first, third and fourth relapses. The material was obtained by continuous extraction, usually for ninety minutes, after subcutaneous administration of histamine phosphate. The gastric juice was divided into fractions for each fifteen minute interval. The lowest p_H, as well as the presence of free hydrochloric acid, with Töpfer's reagents as indicator, are recorded in table 5. During the fourth relapse the test was repeated daily for five successive days. The juice at this time was obtained by suction at a regulated negative pressure of 10 cm. of mercury and was not fractionated.

It will be noted that the absolute achlorhydria, with a neutral p_H after stimulation with histamine, which had existed as late as the first remission, failed to persist. The initial specimen of gastric juice extracted during the fourth relapse showed an absence of free hydro-

TABLE 5.—*Gastric Acidity Following Stimulation with Histamine*

Period	Erythrocytes, per Cu. Mm.	Weight of Patient, Kg.	Histamine Phosphate Administered, Mg.	Volume of Gastric Juice, Cc./90 Min.	Free Acidity	Lowest p_H
First remission.....	4,510,000	12.3	0.20	25	—	7.6
First relapse.....	2,960,000	16.4	0.25	32	+*	1.2
	2,360,000	16.6	0.25	36	+†	1.2
Third relapse.....	2,410,000	18.4	0.25	40	+	1.8
Fourth relapse ‡.....	2,840,000	27.3	0.50	35	—	4.5
			0.45	50	+	1.8
			0.45	90	+	1.8
			0.45	115	+	1.8
			0.45	90	+	1.8

* Titratable acidity was measured and found to be equivalent to 27 cc. tenth-normal hydrochloric acid per hundred cubic centimeters.

† Titratable acidity in this instance was equivalent to 52 cc. tenth-normal hydrochloric acid per hundred cubic centimeters.

‡ The figures for the fourth relapse represent the data obtained by repeating the gastric extraction on each of five successive days.

chloric acid in the secretion, but the p_H of 4.5 disproved the existence of anacidity. It is interesting that daily repetition of the histamine injections resulted in a more than threefold increase in the volume of gastric juice, as well as in an increased outpouring of hydrochloric acid. It is clear, therefore, that a permanent primary gastric anacidity, such as is characteristic of pernicious anemia in the adult, was not present. One may conclude that the early achlorhydria was a manifestation of a secondary and temporary atrophic change resulting from a deficiency of antianemic material in the tissues.

Demonstration of the lack of intrinsic factor in the gastric juice was accomplished when the child was in her fourth relapse. At this time she was 8½ years of age, and collection of suitable amounts of gastric juice was easily effected. The test subject was a white man, aged 67, who was admitted to the Kings County Hospital, Brooklyn.

in February 1940.[12] His condition was in all respects typical of pernicious anemia, and he had not received any form of liver therapy in many months. Preliminary studies of the patient revealed hyperchromic, macrocytic anemia with 9.3 Gm. hemoglobin, 2,050,000 erythrocytes per cubic millimeter and a color index of 1.5. There was absence of free hydrochloric acid in the gastric secretions after subcutaneous injection of histamine, and the sternal marrow was observed to be typically megaloblastic (fig. 9 *C* and *D*).

The Reimann technic[13] was employed in carrying out the test. The method is based on the observation that small, therapeutically ineffective amounts of fresh liver exhibit a twentyfold to thirtyfold enhancement of antianemic potency after digestion with normal gastric juice.

Twenty grams of raw calf's liver was minced and ground in a mortar and was then mixed with 20 cc. of the gastric juice to be tested. Concentrated hydrochloric acid diluted with an equal volume of water was added to adjust the p_H to 3.5. The mixture was incubated at 37.5 C. for two hours, during which time the p_H was occasionally checked with bromphenol blue to assure a constant value of 3.5. The digested material was then cooled and pressed through a wire mesh sieve, and sodium hydroxide was added to bring the p_H to 5. Approximately 100 to 150 cc. of tomato juice, together with small amounts of lemon juice and seasoning, was added to the final mixture to make it palatable. This liquid was fed to the test subject daily. It was taken on a fasting stomach, and food was withheld for one hour thereafter.

During the initial period, of eleven days, 20 Gm. of liver digested with the child's gastric juice was administered daily. Then followed a second period, of twelve days, during which the test subject received daily a like amount of liver digested with the presumably normal gastric juice of a 9 year old patient with mongolism.[14]

The results of the test are graphically shown in figure 11. It will be observed that the initial period revealed an absence of the hematopoietic activity of the gastric juice. A reticulocyte crisis failed to occur, and the erythrocytes, which showed a value of 1,650,000 per cubic millimeter at the beginning of the test, numbered 1,730,000 at the conclusion of the period. This result was in contrast with the observations during the second period, when normal gastric juice was employed. The reticulocyte curve exhibited a characteristic rise, with

12. Dr. John H. Crawford, then director of the Medical Service, Long Island College Division of the Kings County Hospital, permitted me to conduct the studies on this patient.

13. Reimann, F., and Weil, R.: Ueber den Nachweis des Castleschen Fermentes; Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, Ztschr. f. klin. Med. **126**:568, 1934.

14. This child was convalescing from an infection of the respiratory tract, and his blood showed normal hemoglobin and erythrocyte values.

a peak of 6.7 per cent on the seventh day. At the end of the period the erythrocytes had risen to 2,780,000. It may be added that the subject experienced a renewed sense of well-being and exhibited a striking increase in appetite toward the end of this period.

Intestinal Function During Relapse.—Because it is at times exceedingly difficult to distinguish clinically between primary pernicious anemia and the form which is secondary to sprue, attention was directed to a study of intestinal function. Absorption of dextrose, fat and nitrogen from the intestine was determined during the third relapse after the glossitis and atrophy of the tongue, as well as the anemia, were established. In addition, roentgenographic observations of the gastrointestinal tract were made during this period.

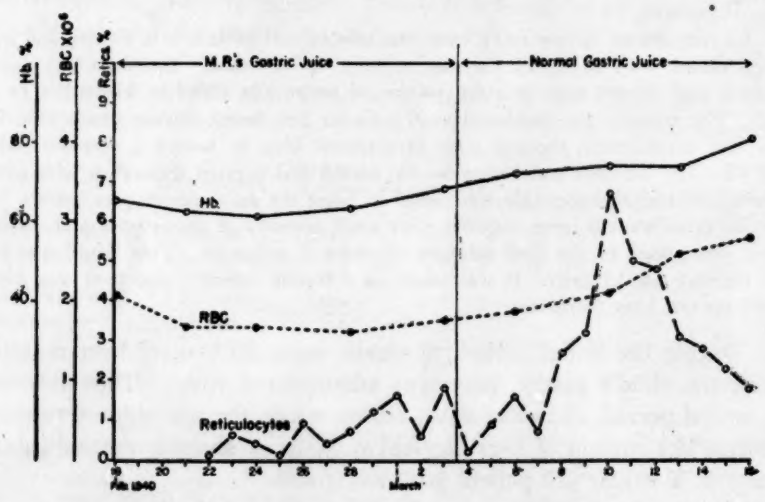

Fig. 11.—Results of test for presence of the intrinsic factor in M. R.'s gastric juice. The Reimann technic[13] was employed, and the test subject was a man 67 years of age with addisonian pernicious anemia in relapse. Administration of the gastric digest was begun on Feb. 22, 1940.

The dextrose tolerance curve after ingestion of 50 Gm. of dextrose was found to be normal (table 6).

In order to carry out studies on fat balance, it was necessary to readmit the child to the hospital. This was done in March 1935. She was given a simple diet in which the sole source of fat was reconstituted powdered whole milk. Because of pronounced anorexia, the child took an average of 716 cc. of milk daily, supplemented with fruit juice and hard candy. Analyses of the stools were made on the material collected during the last four of the eight days that the patient was fed the prescribed diet. The pertinent data are given in table 7.

It will be observed that the excretion of fat in the stools averaged 1.3 Gm. per day. This amount represented 24.1 per cent of the weight of the dried feces. The calculated retention of fat was 96 per cent, a figure differing notably from values found in cases of the various types of steatorrhea. Absorption of nitrogen was of a similar order of magnitude. It is thus clear that the intestinal tract functioned normally with respect to absorption of dextrose, fat and protein.

The roentgenologic examination of the intestinal tract consisted in hourly studies following administration of a barium sulfate meal. It failed to disclose any evidence of malformation, anomaly or stricture. The stomach filled well and emptied within two hours. The barium compound entered the cecum in less than four hours, and the small bowel exhibited normal mucosal patterns. There was no evidence of

TABLE 6.—*Dextrose Tolerance*

Date	Body Weight, Kg.	Erythrocytes, per Cu. Mm.	Dextrose Ingested, Gm.	Blood Sugar, Mg. per 100 Cc.				
				Fasting	30 Min.	60 Min.	90 Min.	120 Min.	150 Min.
3/28/35	18.4	2,450,000	50	115	154	183	137	123	121

TABLE 7.—*Loss of Fat and Nitrogen in the Feces During Relapse**

	Moist Weight, Gm.	Dry Weight, Gm.	Total Fat, Gm.	Fatty Acids, Gm.	Soaps, Gm.	Neutral Fat, Gm.	Nitrogen, Gm.
Diet, per day.....	....	...	32.3	....	....	....	5.1
Feces, per day.....	25.5	5.4	1.3	0.46	0.60	0.24	0.55
Absorption, per cent..	....	...	96	....	....	....	94 †

* Determinations were made during the third relapse, at which time the body weight was 18.4 Kg. and the erythrocytes numbered 2,410,000 per cubic millimeter.

† The calculation was based on an assumed metabolic nitrogen in the feces equal to 0.23 per cent of dry matter of food (115 Gm. milk powder) (Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams & Wilkins Company, 1940, p. 906).

abnormal segmentation or of a change in the muscular tonicity of the intestinal loops. The large bowel was observed to fill and practically to empty within twenty-four hours.

Despite these data indicating normal intestinal function, evidence was obtained during the same relapse of a temporary failure of absorption of the active principle required for maturation of red cells. The information came to light in the course of a first, unsuccessful test for the intrinsic factor in the gastric juice. As in the later test, which has already been described, the Reimann technic was employed. The method differed, however, in that the patient herself was the test

subject.[15] The smallest amount of liver which Reimann found effective, namely, 10 Gm., digested in vitro with the patient's own gastric juice, was fed daily for twelve days. This period was followed by a second one, of eleven days, during which the liver administered was previously digested with the gastric juice of a normal child. Contrary to expectation, no evidence of a hematopoietic response was obtained during the latter period. The erythrocytes numbered 2,620,000 per cubic millimeter at the beginning of the test. There was no increase of reticulocytes during the first period, and the level of erythrocytes was 2,560,000 per cubic millimeter on the eleventh day. A similar lack of response characterized the second period, at the end of which the red blood cells had fallen to 2,100,000 per cubic millimeter. A third period, of thirteen days, followed, during which the child received 12 capsules

TABLE 8.—*Hematopoietic Effect of Parenteral and Oral Liver Therapy*

Date	Body Weight, Kg.	Therapy	Initial Erythrocyte Level / Cu. Mm.	Time Required to Attain 4,000,000 Red Blood Cells, Days	Rate of Regeneration of Erythrocytes /Cu. mm. /Day	Time Required to Correct Hyperchromia, Days	Increase in Body Weight at Attainment of Normochromia, per Cent
March 1933	8.5	Liver extract, 12 cc.	2,040,000	27	73,000	80	55
Feb. 1934	16.6	Liver extract, 3 cc.	2,150,000	32	58,000	39	9
Oct. 1934	18.4	Liver extract, 6 cc.	2,910,000	21	52,000	34	3
April 1935	18.8	Liver extract, 6 cc.	2,260,000	32	54,000	19	1
May 1939	24.8	Liver, 50 Gm. daily given orally for 12 days	2,080,000	..	9,000	..	..
Dec. 1939	27.3	Liver, 100 Gm. daily given orally for 85 days	2,000,000	42	33,000	85	.9

of a commercial liver-stomach concentrate ("extralin") orally each day. At the conclusion of this phase the erythrocyte count was 2,260,000 per cubic millimeter. Since the patient had thus received potentiated liver therapy equivalent to approximately 250 Gm. of fresh liver daily for twenty-four days without improvement, it seemed fair to conclude that there was inadequate absorption of the antianemia principle from the alimentary tract at this time. This interpretation was substantiated by the prompt and rapid rise in blood values which occurred when liver extract was again administered by injection (table 8).

Hepatic Function.—Demonstration of the prolonged antianemic effect of a single injection of liver extract would appear to constitute strong

15. Reimann, F.; Salus, F., and Weil, R.: Das Verhalten des Castleschen Fermentes bei der Anaemia perniciosa und bei den aplastischen Anämien; Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, Ztschr. f. klin. Med. **126**:579, 1934.

evidence that defective hepatic storage was not a factor in the pathogenesis of the anemia. Nevertheless, it seemed desirable to carry out a series of hepatic function tests to support this conclusion. The studies were done in 1946, during a period of remission maintained by the injection of 15 U.S.P. units of liver extract at intervals of four weeks.

The results, all of which were normal, are summarized in table 9. They clearly corroborate the impression that the child did not have dysfunction of the liver.

Therapeutic Response to Liver.—(*a*) Erythrocytes: The efficacy of liver, or of liver extract, in the treatment of the relapsed state was repeatedly tested. The data, which afford a comparison of the

TABLE 9.—*Tests of Hepatic Function**

A. Level of chemical substances in blood	
Total serum protein	6.8 Gm./100 cc.
Albumin	4.28 Gm./100 cc.
Albumin : globulin ratio	1.70
Cephalin flocculation test	Negative result
Thymol turbidity	1.0 Maclagan units
Total cholesterol	187 mg./100 cc.
Free cholesterol	18.7% of total cholesterol
Cholesterol esters	81.3% of total cholesterol
Serum bilirubin	
Direct van den Bergh reaction	Negative
Indirect van den Bergh reaction	0.5 mg./100 cc.
Alkaline phosphatase	4.2 Bodansky units
B. Functional responses with test substances	
Dextrose tolerance †	
Galactose tolerance (40 Gm. orally)	No urinary sugar (5 hr. collection)
Synthesis of hippuric acid—sodium benzoate (6.0 Gm. orally)	
Hippuric acid excreted in 4 hr.	2.9 Gm.
Sulfobromophthalein sodium U. S. P. (2 mg./Kg. intravenously)	No retention after 25 min.

* Tests were conducted during 1946, when the patient was 15 years of age.
† A dextrose tolerance test, performed earlier, is recorded in table 6.

results following parenteral and oral therapy, are summarized in tables 9 and 10 and in figure 12. The reticulocyte response was determined on three occasions, twice after injection of liver extract and once during a period of inadequate oral therapy. A characteristic rise of reticulocytes was observed in the first two instances, but failed to occur when the child was taking liver by mouth. The injection of a single dose of concentrated extract in amounts representing material obtained from 100 to 400 Gm. of liver sufficed on four separate occasions to bring about a complete remission. Similarly, the daily oral administration of 100 Gm. of cooked liver was followed by a satisfactory reestablishment of normal blood values. On the other hand, a daily dose of 50

Gm. of cooked liver taken orally for twelve days was ineffective in this respect.

The rate of regeneration of erythrocytes after parenteral injection of liver extract varied from 52,000 to 73,000 per cubic millimeter per day, with initial levels of 2,000,000 to 3,000,000. When oral therapy was employed, the rate of increase of red cells amounted to 33,000 per cubic millimeter per day. It is apparent that, in the dose employed, oral therapy resulted in a slower hematopoietic response. Nevertheless, complete remission was attained with this method.

The effectiveness of treatment in maintaining a normal hematologic status was tested during periods ranging from five months to almost six years (table 11). Monthly injections of 15 U.S.P. units of a concentrated liver extract were found to be entirely adequate, as was the daily ingestion of 100 Gm. of cooked liver. Oral liver extract was employed for a short period, with satisfactory results. The initial

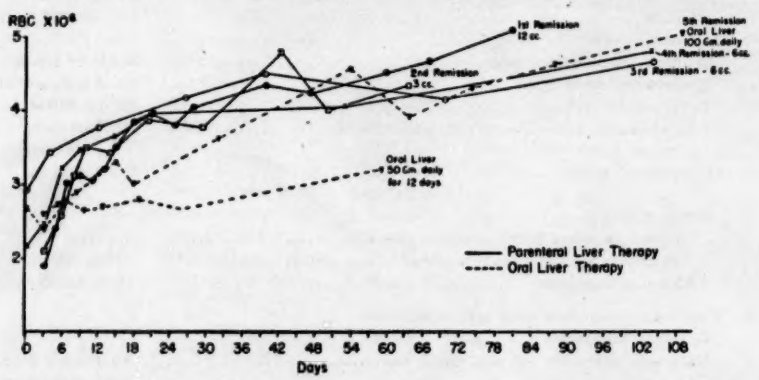

Fig. 12.—Comparison of the effectiveness of oral and parenteral administration of liver in treatment of relapses.

and final values for erythrocytes and hemoglobin are recorded in the table as representative figures. With the exception of a three year lapse during the war, the success of maintenance therapy was constantly checked by frequent blood counts.

(*b*) Effect of Treatment on Variability of Erythrocytes: Judged on the basis of hemoglobin values, erythrocyte counts and determinations of color index and mean corpuscular volume, patients with pernicious anemia respond satisfactorily to the administration of adequate amounts of liver or liver extracts. That many of these patients fail to attain complete normality of the blood picture is evident, however, from the fact that the variation in size of their erythrocytes exceeds that of the erythrocytes of healthy persons. This fact was demonstrated by Price-Jones,[9] who measured the red cell diameters of 12 patients with pernicious anemia before and after treatment. The method of

study which he employed yields information concerning three aspects of the size of erythrocytes—the mean diameter, the degree of variability of the diameters and the percentage of cells whose diameters fall outside the limits observed in normal blood. Although commonly employed in the determination of the mean diameter of red cells, the method is of particular value in that it is the only one which permits mathematical expression of the degree of anisocytosis of the erythrocytes.

TABLE 10.—*Reticulocyte Response to Liver Therapy**

Days	Liver Extract, 12 Cc.: Reticulocytes, per Cent	Liver Extract, 3 Cc.: Reticulocytes, per Cent	Cooked Liver, 50 Gm. by Mouth Daily: Reticulocytes, per Cent
0	1.4	1.7	0.2
1	3.3	0.5	0.0
2	10.0	1.7	0.3
3	16.8	4.8	0.2
4	19.6	17.0	0.3
5	21.6	24.1	0.7
6	42.4	3.2	0.7
7	14.4	...	0.7
8	13.1	2.3	1.2
9	7.9	1.9	0.9
10	...	...	0.4
11	5.6	...	0.2
12	...	...	0.1
13	5.1	...	0.2

* Data with respect to initial erythrocyte levels are shown in table 8.

TABLE 11.—*Efficacy of Maintenance Therapy*

Therapy	Date Initiated	Duration	Initial Blood Levels: Hemoglobin, Gm.	Initial Blood Levels: Erythrocytes/Cu. Mm.	Final Blood Levels: Hemoglobin, Gm.	Final Blood Levels: Erythrocytes/Cu. Mm.
Parenteral injection of liver extract, 1 cc. at monthly intervals	June 1935	2 yr. 5 mo.	12.0	4,000,000	13.7	4,740,000
Daily oral administration of liver extract obtained from 600 Gm. liver	Nov. 1937	5 mo.	13.7	4,740,000	12.2	4,790,000
Daily oral administration of liver, 100 Gm., cooked	Mar. 1940	5 yr. 9 mo.	13.3	4,320,000	13.3	4,260,000

Moreover, according to Price-Jones, the degree of anisocytosis, expressed as a coefficient of variation, is important because "it is probably the most delicate test for a departure from normal in red cell diameters."

It seemed desirable to apply the standards set by Price-Jones as a test of the normality of the child's red blood cells at a time when, by all other criteria, remission was completely established. The technic consisted in projecting the images of the erythrocytes at a magnification of 1,000 and recording the average of the smallest and greatest diameters of each of 500 cells. The results of such an analysis are set forth in

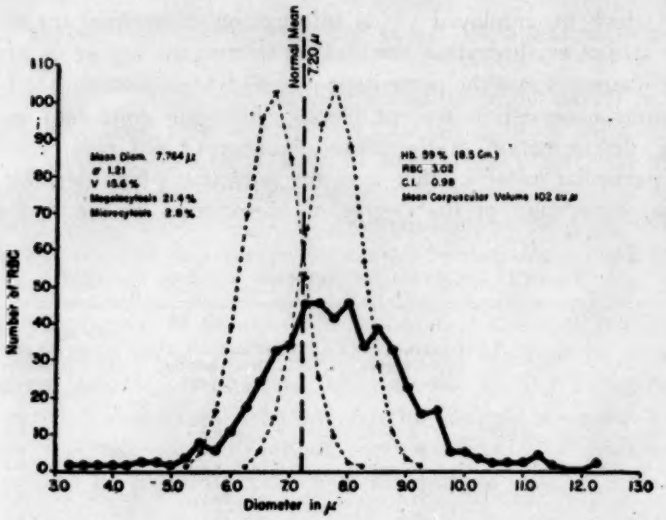

Fig. 13.—Price-Jones curve for erythrocytes shortly after specific treatment of the initial illness was instituted. Curves of reference representing the extremes of normal are indicated by broken lines.

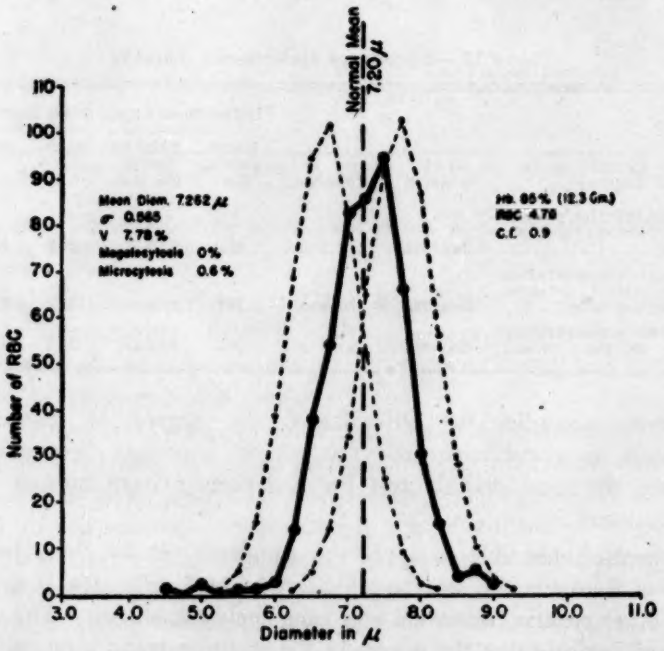

Fig. 14.—Price-Jones curve for erythrocytes during remission.

figures 13 and 14 and in table 12. The erythrocytes were studied in September 1942, at the end of a period of nearly two years during which the cells were maintained at high levels by the daily ingestion of 100 Gm. of cooked beef liver. The data may be compared with those obtained in 1933, in the initial phase of a period of remission.[16] During the latter period the blood exhibited all the features characteristic of pernicious anemia. The mean diameter of the red cells, 7.764 microns, was outside the limits of normal set by Price-Jones. Values for the standard deviation and the coefficient of variation were more than twice those for normal blood, and megalocytosis, as well as microcytosis, was present. All these values were significantly changed during the period of completely established remission. It may be noted that the plotted curve now indicated a fairly normal distribution of erythrocytes with respect to size. Moreover, the mean diameter had

TABLE 12.—*Variability in Size of Erythrocytes in Pernicious Anemia**

	Mean Diameter, Microns	Standard Deviation, Microns	Coefficient of Variation, per Cent
Normal			
Average	7.202	0.46†	6.3
Limits (average ±3σ)	6.686-7.718	0.38-0.53†	5.3-7.3
Pernicious anemia in relapse			
Average	8.31	1.08†	13
Observed range	7.487-9.673	0.75-1.32†	8.3-18.8
Pernicious anemia treated			
Average	7.54†	0.54†	7.1†
Observed range	7.265-7.939	0.43-0.68	5.7-8.7
M. R.			
In relapse	7.764	1.21	15.6
In remission	7.262	0.57	7.8

* Normal values are those reported by Price-Jones[9] and represent data obtained for 100 healthy persons. Values for pernicious anemia are those reported by the same author.
† Values calculated from data of Price-Jones.

decreased to the normal value of 7.262. Megalocytosis had entirely disappeared, but a minimal degree of microcytosis persisted.

The question of the normality of the curve as an expression ot the data obtained during a period of apparently complete remission can be answered only by a consideration of the standard deviation and the coefficient of variation. In measurements of the red cells of 100 normal men and women, Price-Jones obtained values for the standard deviation of erythrocyte diameters ranging from 0.41 to 0.53. From these figures the mean value of 0.46, with a standard deviation of 0.026, was calculated. The mean value ± 3 times the standard deviation set 0.38 to 0.53 as the limits of normal. Similarly, the values for

16. Blood films were obtained one week after the first treatment of the patient with liver extract. During this interval the erythrocytes had increased from 2,040,000 to 3,020,000 per cubic millimeter, and the hemoglobin, similarly, had risen from 40 to 59 per cent.

the coefficient of variation were observed by Price-Jones to be between 5.6 and 7.3 per cent, with a mean value of 6.3 per cent and a normal range of 5.3 to 7.3 per cent. The corresponding values for the patient here described during the period of remission, namely, standard deviation, 0.57 and coefficient of variation, 7.8 per cent, although manifesting a striking degree of correction of the preexisting abnormality, nevertheless fall just outside the limits for the blood of healthy persons. It should be noted that these values are in close agreement with those found by Price-Jones for adult patients with pernicious anemia after treatment (table 12). One may conclude from these values that the improvement in the patient's blood after liver therapy fell short of a complete return to normal.

(*c*) Leukocytes; Platelets; Bone Marrow: The leukocytic response was studied after the initial treatment with intramuscular administration of liver extract. Leukocytosis, with a count of 14,000, affecting all the formed elements, was observed on the third day. It was accompanied with the appearance of myelocytes, as well as normoblasts, in moderate numbers. The thrombopenia was abolished in one week. After the first week the only abnormality was a striking eosinophilia. The eosinophils rose to 29 per cent of 12,000 leukocytes during the fourth week. The eosinophil count remained elevated, with values usually ranging from 700 to 2,000 per cubic millimeter, during the succeeding ten months. That eosinophilia of pronounced degree may follow the ingestion of raw, or partially cooked, liver has been known for many years.[17] Few instances of the appearance of the phenomenon after the parenteral administration of liver extract, however, have been reported. The literature on this subject has recently been reviewed by Hanno and Mensh.[18]

Data reflecting the changes in the bone marrow are given in table 3 and have already been discussed.

Absence of Therapeutic Response to Nicotinic Acid and Riboflavin.—An attempt was made during the fourth relapse to determine whether the glossitis was a manifestation of pellagra or of riboflavin deficiency. At the same time, the hematopoietic effect of large amounts of nicotinic acid and riboflavin was compared with that observed after oral administration of liver in amounts containing only a fractional dose of these vitamins. The exact timing of the tests was dictated by the presence of glossitis of sufficient severity to facilitate interpretation of the results. Nicotinic acid was administered orally during four test periods over

17. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: A Study of One Hundred and Five Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

18. Hanno, H. A., and Mensh, M.: Eosinophilia Following Parenteral Liver Therapy: Literature and Case Report, Am. J. M. Sc. **209**:572, 1945.

an interval of twelve months. Evidence of satisfactory absorption was afforded by the transient flushing of the skin which was regularly observed after the tablets were swallowed. The first period lasted thirty-four days. Nicotinic acid U.S.P., in 50 mg. amounts, was given daily for seven days, after which the dose was increased to 100 mg. During the second period 100 mg. was given daily for thirteen days. During the third period 300 mg. was given daily for sixteen days. The fourth period was one of combined vitamin therapy for sixteen days. Nicotinic acid, 300 mg., was given daily for eight days, followed by administration of 400 mg. daily for four days. Simultaneously, riboflavin U.S.P. in increasing doses of from 5 to 25 mg. daily was administered. During this period, also, 10 mg. of thiamine hydrochloride U.S.P. was incorporated in the daily vitamin intake. Cooked beef liver was administered during two test periods. During the first of these periods, 50 Gm. of liver was ingested daily for twelve days, while during the second the dose was 60 Gm. daily for ten days.

Nicotinic acid, either alone or in combination with riboflavin and thiamine hydrochloride, was without detectable effect on the fluctuating severity of the glossitis. On those occasions on which slight improvement in the inflammatory reaction was observed, the favorable effect was usually succeeded by atrophic, rather than regenerative, changes in the papillae. In contrast to this condition was the definite amelioration of the glossitis which followed the ingestion of small amounts of cooked liver. At the beginning of the second period of this form of therapy, the soreness of the tongue was severe enough to interfere seriously with eating. Within three days striking improvement occurred and all subjective symptoms disappeared. Minor residual inflammatory changes, however, persisted at the conclusion of each of the test periods.

Despite the beneficial effect on the tongue, as well as the subjective improvement, which followed the daily ingestion of liver in amounts of 50 Gm., it at first appeared that there was no accompanying hematopoietic response. During a period of twenty-six days repeated blood counts revealed the absence of a reticulocyte response, as well as the lack of a significant change in the erythrocyte level or in the hemoglobin content. However, when the data for all test periods were plotted with respect to the line of regression expressing the calculated rate of decline of the erythrocytes during relapse, an interesting result was obtained (fig. 15). It may be noted that during the first two periods of nicotinic acid therapy the erythrocytes continued to fall at the expected rate. On the other hand, the oral administration of liver resulted in an immediate and sustained departure from the line of regression. When the effect of the two periods of liver therapy wore off, the erythrocyte level began once more to decline in an exactly predictable manner. Again, the administration of large amounts of

nicotinic acid, as well as of riboflavin and thiamine hydrochloride, failed to exert the slightest influence on the downward trend.

Growth and Development.—The influence of disease and of therapy on the rate of growth from infancy to adolescence is graphically represented in figures 16 and 17. The data for height and weight are plotted against curves expressing average normal standards for girls. During the initial illness the complete cessation of growth as measured by body length is clearly shown. A similar, though less pronounced, effect of illness is apparent also during the fourth relapse (fig. 17), which was the longest in duration. Here, a retardation in rate of growth is evidenced by a drop in the curve below the normal standard. The first, second and third relapses, in which abnormal erythrocyte levels were present for periods up to five months, did not appear to affect the upward trend of the curve for height.

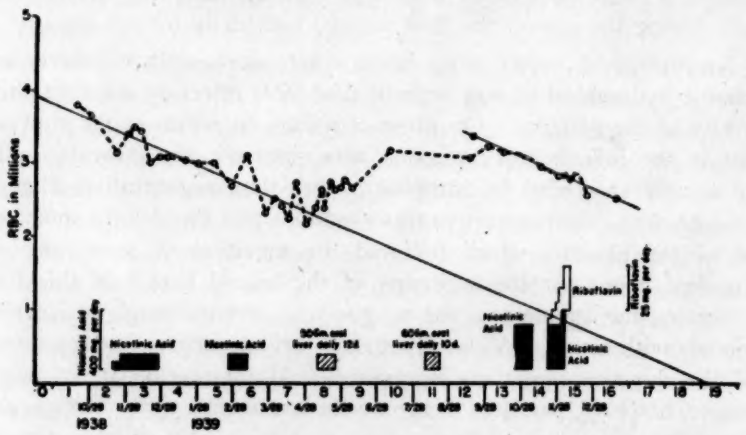

Fig. 15.—Effect on declining erythrocytes of nicotinic acid, riboflavin and oral administration of suboptimal amounts of liver. The long unbroken line is regression line *1* from figure *7*. The short unbroken line has been constructed parallel to this regression line.

A compensatory acceleration of growth following liver therapy is seen to have occurred after each of the two periods of retardation. In the first period, a striking increase in rate of growth was maintained for eleven months after a single dose of liver extract administered parenterally. On the second occasion, a similar effect was observed after treatment of the fourth relapse with oral ingestion of liver. This increase was succeeded, in turn, by the normal acceleration of growth during puberty.

The curve for weight exhibits trends similar to those of the curve for height, but with somewhat greater fluctuations. Gains in weight, though slowed by increasing anemia, tended to continue during relapse. Actual loss of weight is seen to have been a late manifestation of the

initial illness. Clearly evident also are the pronounced and rapid increases in body weight following treatment with liver or liver extract. After the initial illness there was a period of moderate obesity lasting for two and one-half years. During this period the curve is approximately 20 to 30 per cent above the normal standard. The curve in general tends to remain elevated during most of childhood, after which it drops, approaching the normal standard closely during adolescence.

Additional observations in connection with the development of the patient may be cited at this point. The appearance of secondary sex

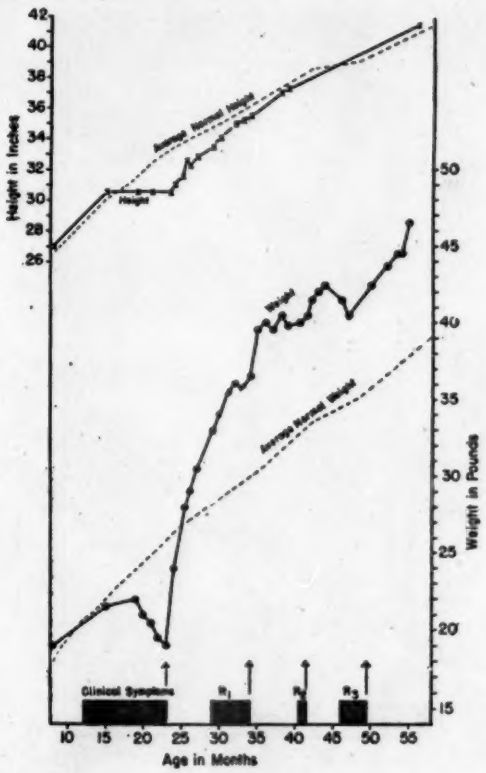

Fig. 16.—Curves for height and weight in relation to periods of illness during the first five years of life. *R* indicates time and duration of relapses. Parenteral administration of liver extract is indicated by arrows.

characteristics was noted at 11 years (fig. 18). The menarche had its onset just before the thirteenth birthday and was followed by normal menstruation thereafter. Mental development appeared to be normal in all respects. The child made satisfactory progress at school and at the age of 16 was performing her work well in the third year of high school. Resistance to infection was entirely normal. The child survived the usual infectious diseases, including pertussis, chickenpox, measles,

mumps and scarlet fever, without complications and without a depressing effect on the blood picture. Sulfathiazole was well tolerated and proved effective in the treatment of a suppurative frontal sinusitis, contracted at the age of 10. Dentition was poor, and numerous cavities appeared in the deciduous teeth, which seemed to be imperfectly calcified. The child did not have to undergo any surgical operation.

An untoward and psychologically disturbing manifestation of her disease was the appearance of a few gray hairs when the child was 8 years of age. This condition slowly, but steadily progressed and

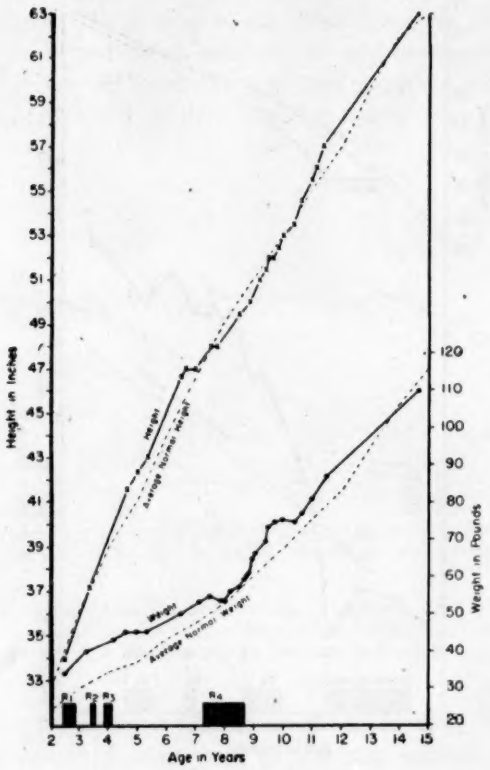

Fig. 17.—Physical development during entire period of study. *R* indicates time and duration of relapses.

in the course of a few years became readily noticeable and was a subject for comment. The gray hairs were scattered throughout the scalp but were more in evidence over the back of the head. It may be of significance that the graying of the hair began in the course of the fourth, and most prolonged, relapse. Unfortunately, the subsequent remission, which was in other respects satisfactorily maintained for six years by daily oral liver therapy, was not accompanied with a favorable change in the condition of the hair. Parenteral administration

of liver extract (15 U.S.P. units injected once every four weeks) was substituted for oral therapy at the age of 14½ years and has thus far been maintained for fourteen months. Although this interval is too short for more than tentative deductions, there is a suggestion that the increasing grayness of the hair has been halted.

Familial Incidence of Anemia.—It has been mentioned previously that an older sibling died of a similar disease. The record of the case was fortunately available and is presented here for purposes of comparison.

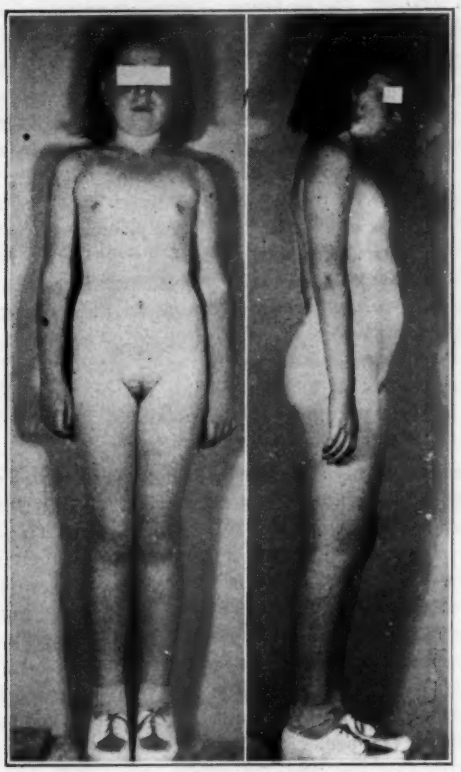

Fig. 18.—Photographs of M. R. showing physical development at 11 years of age. The height at this time was 57 inches (145 cm.) and the weight 86 pounds (39 Kg.). Partial graying of the hair which was present is not visible in these photographs.

REPORT OF CASE OF PATIENT'S SIBLING

S. R. a boy, was born in April 1926, weighing 6 pounds 12 ounces (3,062 Gm.). He was breast fed for nine months and received supplementary feedings of cow's milk. Orange juice was added to the diet at 5 months; cereals, vegetables and zwieback at 6 months, and meat and fresh fruits at 12 months of age. He sat unsupported at 5 months and his first teeth erupted at about 6 months of age. At 1 year of age he weighed more than 20 pounds (9,072 Gm.). He stood alone

at 15 months and walked at 16 months. The first symptoms of his illness began in January 1928, at the age of 21 months. After an attack of tonsillitis at this time, anorexia developed, persisting with increasing severity until the time of his death, ten months later. In March 1928 he began to vomit frequently. Diarrhea gradually developed, which was intermittent. The stools at first were formed and of normal color but were more frequent than normal. They would then become watery for a time, after which the symptoms would subside. His general condition would improve for a short period, only to relapse when his gastrointestinal difficulties recurred. As a result of increasing weakness he refused to walk or stand. After a relatively good period following measles in May 1928 he had a severe exacerbation in July. At this time his temperature was elevated to 103 to 104 F., his mouth was sore, and he began to manifest an increasing pallor. During the next few weeks he lost 4 pounds (1,814 Gm.) in weight.

In August 1928 he was admitted to the Babies Hospital in New York because of anorexia, vomiting and loss of weight.[19] The infant was not acutely ill but appeared weak and apathetic. His skin was loose and inelastic, and there was little subcutaneous fat. Examination of his blood revealed a hemoglobin level of 34 per cent with 1,410,000 red blood cells per cubic millimeter. The leukocytes varied from 2,000 to 4,300, "with a normal differential" count. The platelets numbered 248,000 per cubic millimeter. Moderate albuminuria and slight cylindruria were present. The icteric index was 18.8 units; the direct van den Bergh test gave a negative immediate reaction and a delayed reaction of 2 plus. The reaction to the intradermal test with tuberculin was negative. The dextrose tolerance curve was flat. The infant received a transfusion of 190 cc. of blood. He remained in the hospital for two and one-half weeks, during which time the highest hemoglobin concentration was 40 per cent and the highest red cell count 2,670,000 per cubic millimeter. His appetite continued to be poor, but he gained 300 Gm. during his stay.

Since improvement of his condition was not maintained, he was taken to a second hospital, where he remained for six weeks. During this time he received two blood transfusions. In November 1928, at 31 months of age, he was admitted to the Jewish Hospital. Additional information elicited in the history taken at this time was that the child's stools had never shown evidence of blood or mucus. There was, moreover, nothing in the history suggesting ingestion of lead or exposure to other toxic substances. Examination revealed that he was an emaciated apathetic infant with dry, wrinkled skin and extreme pallor of the mucous membranes. The hair was noted to be fine, dry and sparse. The reflexes were normal; there was no glandular enlargement, and the liver and spleen were thought to be of normal size. The hemoglobin concentration (Dare) was 30 per cent; the red cells numbered 1,690,000 and the white cells 1,800, per cubic millimeter, with a differential count of 26 per cent polymorphonuclear neutrophils, 65 per cent lymphocytes and 7 per cent monocytes. There were 2 megaloblasts per hundred leukocytes, and the erythrocytes showed pronounced anisocytosis, poikilocytosis and polychromasia. The platelets numbered 80,000 per cubic millimeter, and there was no clot retraction after ninety-six hours. Moderate albuminuria and cylindruria were present. The Wassermann and Kahn reactions were negative. The van den Bergh test gave a negative direct reaction and a positive indirect

19. An abstract of the clinical data with respect to this admission was kindly sent to the Jewish Hospital when the infant subsequently was brought there as a patient.

reaction of 1 unit. The icteric index was 6 units. Examination of the stools failed to reveal ova or parasites, and a culture was negative for dysentery organisms.

Treatment consisted of two blood transfusions of 200 and 150 cc., respectively, given at an interval of five days. After the first of these transfusions the hemoglobin level rose to 58 per cent and the red cells numbered 3,450,000 per cubic millimeter. There were at this time 2,100 leukocytes per cubic millimeter, of which polymorphonuclear neutrophils formed 8 per cent, eosinophils 9 per cent, lymphocytes 73 per cent, monocytes 6 per cent and myelocytes 4 per cent. On the child's sixth day in the hospital, the temperature, which had previously been normal, rose to 101.2 F. Signs of pneumonia involving the lower lobe of the right lung appeared, and the child died on the following day. An autopsy was not performed.

COMMENT

During the interval of twelve years since the preliminary report of this work was published,[2] there has been a significant increase in knowledge with respect to the hyperchromic macrocytic anemias of infancy. It has now been amply demonstrated that there occurs in infants an anemia responding specifically to treatment with liver extract or with folic acid.[20] Although the origin of the deficiency remains obscure, those published reports which have included details of the subsequent clinical course have made it clear that the therapeutic result is one of complete and permanent recovery. From this type of anemia one must differentiate a second, in which, despite a satisfactory dietary intake and absence of primary intestinal disease, continuous liver therapy is essential for maintenance of normal hematopoiesis. The present case (M. R.), as well as 3 other cases subsequently reported by Dedichen,[21] Jonsson [22] and Peterson and Dunn,[20c] fall into this category.

Dedichen's case was that of a male infant of 9 months, whose symptoms had begun about one month earlier. Anemia, achylia (after an Ewald test meal) and a megaloblastic bone marrow were observed. The response to iron therapy was slight, but the injection of liver extract was followed by reticulocytosis and a satisfactory increase in hemoglobin and erythrocytes. Relapses occurred at variable intervals after the discontinuance of parenteral liver therapy and were usually preceded by

20. (*a*) Bachman, A. L.: Macrocytic Hyperchromic Anemia in Early Infancy: Report of a Case and Review of the Literature, Am. J. Dis. Child. **52**:633 (Sept.) 1936. (*b*) Karlström, F., and Nordenson, G.: Hyperchromic (Pernicious?) Anaemia in Infancy, Acta pædiat. **32**:58, 1944. (*c*) Peterson, J. C., and Dunn, S. C.: Pernicious Anemia in Childhood, Am. J. Dis. Child. **71**:252 (March) 1946. (*d*) Zuelzer, W. W., and Ogden, F. N.: Megaloblastic Anemia in Infancy: A Common Syndrome Responding Specifically to Folic Acid Therapy, ibid. **71**:211 (March) 1946.

21. Dedichen, J.: Anémie à type pernicieux chez un enfant de neuf mois, Acta med. Scandinav. **111**:90, 1942.

22. Jonsson, B. J. Pernicious Anaemia in Children, Acta pædiat. **32**:485, 1945.

infection of the respiratory tract. At the time of the last relapse mentioned by the author the child was 4 years of age.

Jonsson reported observations on a male infant with symptoms, beginning at 18 months of age, of pallor, listlessness and diarrhea. Treatment with blood transfusions and iron was unsatisfactory, but injections of liver extract were followed by correction of the profound anemia within one month. The patient was maintained in good health with parenteral liver therapy When this treatment was stopped, at the age of 4 years, and the child failed to take liver extract orally, he relapsed within four months. Reinstitution of parenteral liver therapy at this time resulted in a rapid increase in hemoglobin and erythrocytes, accompanied with a typical increase in reticulocytes. Normal gastric acidity after stimulation with histamine was found.

The most recent case has been described by Peterson and Dunn.[20c] Their patient was a girl, first seen at the age of 13 months, and observed during three relapses, occurring over a period of four years. The information was elicited that 1 of 3 siblings had died at the age of 3 years because of diarrhea and anemia. For treatment of the initial illness, as well as of the first two relapses, repeated transfusions and iron therapy were employed, without lasting benefit. Institution of parenteral liver therapy was followed each time by a characteristic reticulocyte response, as well as by a rapid rise of hemoglobin and erythrocytes. In the absence of therapy relapses regularly occurred, and the time of their appearance seemed to bear some relation to the amount of liver previously administered. Peterson and Dunn reported an absence of free hydrochloric acid in the gastric juice after injection of histamine.

While these cases appear to be examples of persistent deficiency of the antianemia factor, one can only speculate regarding the pathogenesis of the condition and its relation to pernicious anemia of the adult. In the present case (M. R.) evidence is presented indicating that there was a lack of normal antianemic activity of the patient's gastric juice. That the defect in the secretion of the gastric intrinsic factor was primary is supported by the evidence that the anatomic configuration and the patterns of motility of the intestinal tract were roentgenographically normal, that intestinal absorption of fat, dextrose and nitrogen was observed to be normal and that there was no disturbance of storage or utilization in the body of the antianemia principle. Other atrophic or inflammatory changes in the alimentary tract that were present from time to time were clearly of a secondary nature. These included the glossitis, the gastric anacidity and the failure, during one of the relapses, of intestinal absorption of the antipernicious anemia factor. All these changes were specifically reversible with liver therapy.

The condition in this case (M. R.) differed from that in the adult form of pernicious anemia in two important respects. The first was the

lack of permanence of the absolute achlorhydria, an observation which is, however, difficult to interpret in view of the existing lack of knowledge of the role of anacidity in the pathogenesis of the adult disease. The second was that no tendency to the development of spontaneous remissions was discoverable. The latter observation is noteworthy, since in the adult periods of improvement with regeneration of erythrocytes formed one of the most constant features of the disease in the days before the application of specific therapy. Thus, Cabot,[23] in analyzing the course of 647 cases, observed that the progressive deterioration in the great majority of cases was punctuated by one or more remissions. Indeed, he went so far as to state, "The proved absence of remissions in a case of anemia is important evidence that it is not of the Addisonian or truly 'pernicious' type." In this connection one may point out that studies of the initial illness, as well as of the four relapses which the child was allowed to undergo, revealed no departure from certain fixed rates of decline of red blood cell levels. It is possible, therefore, that the distinctive feature of the child's gastric defect is its totality, whereas the breakdown of the gastric antianemic function in adults is incomplete and subject to periods of partial recovery which interrupt the generally downhill trend of the illness.

To pursue further the question of the pathogenesis of the disease, it is of interest to attempt to reconstruct the hematologic course of the initial illness during infancy. It has been shown that relapse invariably followed one of two pathways (figs. 6 and 7). One of these, entailing a rapid fall of erythrocytes, was observed to occur when the body reserves of antianemia principle were presumably exhausted. The other, a more gradual decline of erythrocyte levels, characterized the relapse after prolonged treatment. The regression lines expressing these two rates of fall appear as lines *OA* and *OB* in figure 19. Point *O* denotes the number of erythrocytes observed at 21 months, the age when the child was first seen. Points *A* and *B* mark the intersection of the regression lines with the line representing a level of 4,000,000 red blood cells per cubic millimeter. The age indicated at each of the intersections denotes the time at which the erythrocytes would have begun to decline at the two rates in question.

It will be seen that line *OB* indicates the onset of the initial illness at 18 months. This is not in accord with the history of clinical symptoms observed by the parent to have begun at the age of 12 months. It is possible, however, that the rapid rate of fall may have been taking place for only a short time prior to admission to the hospital and that the actual

23. Cabot, R. C.: Pernicious and Secondary Anemia, Chlorosis, and Leukemia, in Osler, W., and McCrae, T.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 5, p. 51.

course involved an initial period of gradually declining values, succeeded by a terminal precipitous drop. This likelihood finds support in the fact that lines *DE* and *FG*, representing the fall of erythrocytes after transfusions given at this time, are roughly parallel to line *OB*.

Line *OA* places the onset of the disease between 8 and 9 months of age. According to this line, the disease would have been active for about three months, and the erythrocytes would have fallen to a level of 3,250,000 per cubic millimeter before the beginning of clinical symptoms. These suppositions are entirly in accord with the observations which were made during the first and fourth relapses. For comparative purposes, a parallel regression line was plotted with the initial point *A'* at ten months. This line meets *OB* at *C*. If this line correctly represented the

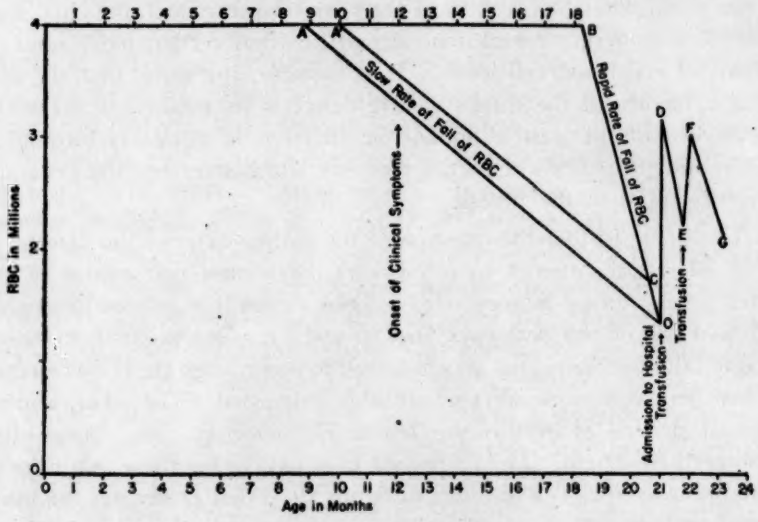

Fig. 19.—Reconstruction of course of initial illness. Lines expressing the rate of progress of the disease are those derived in figure 7.

initial illness, the disease beginning at 10 months would have progressed so that the erythrocytes numbered 3,550,000 per cubic millimeter at the onset of symptoms. At point *C* the rate of decline of red cells would have changed to the more rapid one indicating exhaustion of reserves at the age of 20½ months.

Evidence suggesting that the erythrocytes began to fall when the infant was about 9 months of age takes on added interest in view of the demonstrated capacity of the body to store the antianemia principle. Thus, a single dose of 12 cc. of liver extract was followed by an increase of two and one-half times the number of circulating erythrocytes and the maintenance of normal values for six months. Since it has been shown

that the liver of the fetal calf has a high antianemic potency,[24] it is probable that the human infant is similarly endowed at birth with the materials needed for hematopoiesis. In these circumstances, it is not inconceivable that prenatal stores of antianemia principle could have been sufficient to account completely for the normal development of the infant during the first 9 or 10 months of her life. The interpretation suggested, therefore, is one of congenital absence of the gastric intrinsic factor. The cause would thus be distinct from that encountered in the adult disease.

An alternative interpretation of the origin of the anemia would envisage a degenerative process analogous to that in the adult, with loss of a previously normal capacity to secrete the intrinsic factor. Instead of a gradual, halting process, however, the loss would of necessity have taken place abruptly, and more or less completely, during the first few weeks or months of life. That degeneration with virtual extinction of a function would follow such a course, however, seems physiologically improbable.

SUMMARY

A syndrome is described which is thought to be due to congenital absence of the intrinsic factor in the gastric secretions. It is characterized by an initial period of normal development, during which the infant utilizes the blood-building materials accumulated in its tissues during gestation by placental transmission. After several months a number of symptoms of failing health set in. This period is marked by a slowly progressive fall of erythrocytes and the development of a typical picture of pernicious anemia. The condition did not exhibit the tendency to spontaneous remissions which is characteristic of pernicious (addisonian) anemia in the adult.

555 Prospect Place.

24. Wigodsky, H. S.; Richter, O., and Ivy, A. C.. The Anti-Pernicious-Anemia Factor Is Present in Fetal Calves' Livers; or, the Permeability of the Placenta to the Anti-Pernicious-Anemia Factor. Am. J. Physiol. **123**:215, 1938.

DELAYED ONSET OF "THREE MONTHS'" COLIC IN PREMATURE INFANTS

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SO-CALLED three months' colic, which is manifested by severe, prolonged, paroxysmal crying in infants during the early weeks after birth, is a well recognized problem among practicing physicians. Despite many advances in methods of infant care little has been accomplished toward providing an adequate explanation of the cause of this condition nor has its prevention or treatment been worked out.

It is well recognized that this type of behavior is seldom manifest in nurseries for newborn infants, although some infants seem to give indications of a tendency to colic by their excessive irritability and their unusually large food requirement. These indications are seldom enough to warrant the prognosis of excessive crying after dismissal from the nursery. It has been noted that full term infants frequently begin to cry in increasing amounts a few days after going home from the nursery for newborn infants. In the experience of my colleagues and me, the onset usually occurs when the infant is from 2 to 3 weeks of age. It is well recognized by both physicians and mothers that the symptoms are likely to end spontaneously when the infant is about 3 months of age. This characteristic time of onset and the limited duration of the symptoms would seem to be most adequately explained by considering that a developmental factor is at least partially responsible for the disturbed physiologic mechanism that causes the symptom complex.

Recently, we have observed the course of paroxysmal crying in a number of premature infants. It was noted that the onset was delayed for a period approximately in proportion to their degree of prematurity. This interval was observed even in an infant weighing 2½ pounds (1,124 Gm.) at birth, whose period of hospitalization in the nursery for newborn infants totaled sixty days. A few reports of typical cases are presented.

REPORT OF CASES

CASE 1.—A boy was delivered by cesarean section on March 22, 1946, because of central placenta previa. The weight at birth was 2,140 Gm. The delivery was five weeks prior to the expected date.

From the Section on Pediatrics, Mayo Clinic.

The infant's progress was good while he was in the nursery, and he was dismissed to his home on April 12, weighing 2,500 Gm. On April 17, it was reported that he was doing well and that he cried little. On May 3, when he was seen in the well baby clinic, the mother reported that he cried lustily when hungry One week later, she reported that he cried excessively between feedings and was not satisfied with a large caloric intake.

In this case, the onset of excessive crying was seven weeks after delivery, or two weeks past the date considered to be the full gestation period.

CASE 2.—A boy who weighed 2,330 Gm. was delivered on Sept. 29, 1944. Labor followed premature rupture of the membranes from an unknown cause. The mother's last menstrual period had begun on February 1, and the expected date of delivery was November 8. The infant was dismissed from the nursery on October 21, weighing 2,570 Gm. On October 31, he was reported to be doing well at home, and his crying was moderate in amount. On November 14, six weeks after birth, he began to exhibit excessive crying in the evening. An increase in caloric intake brought about a partial improvement, but the crying persisted in decreasing severity during the next several weeks. When seen on Jan. 10, 1945, he was doing well, and it was reported that he cried little.

CASE 3.—A boy weighing 1,940 Gm. was delivered by breech extraction on May 4, 1946, after a thirty-four week period of gestation. During the period in the infants' nursery, he was noted to be a quiet infant. He was dismissed to his home on June 2, at which time he weighed 2,400 Gm. He got on well at home until about July 1, eight weeks after birth, when he began to cry excessively after feedings. Sedation was prescribed, and it was necessary to continue this medication during the next six weeks.

COMMENT

The foregoing cases are 3 selected from a larger number which have been recently observed. In each case the infant, who previously had been quiet and progressing normally, manifested excessive crying when approximately two weeks older than the expected date of delivery. This behavior was not explainable on the basis of improper feeding technics or hunger. The infants were allowed adequate caloric intake. The crying seemed to appear when the infants reached a certain state of maturity; it was not simply the "awakening process" observed normally as premature infants grow older.

My associates and I have no proved explanation for these observations. Until more is learned about the pathogenesis and pathophysiologic changes in colic, perhaps an adequate answer will not be available. While many views have been expressed as to the most likely cause of the condition, no one of them in itself has proved entiely satisfactory. Such factors as underfeeding, overfeeding, improper feeding technics, gastrointestinal allergy, imbalance of the autonomic nervous system and others are probably partially responsible, either alone or in combination, in many of the cases. Because of the observed time of onset and the duration of symptoms in both full term and premature infants, it is our belief that a developmental factor also contributes to the cause. The

nature of this factor is not known, but it would seem reasonable to assume that it may be primarily related to the state of maturity of some part of the nervous system. Further basic study concerning these points is needed.

SUMMARY

Observations on premature infants in whom symptoms usually referred to as "three months'" colic developed indicate that the onset is usually delayed by an interval commensurate with the period of prematurity. While an adequate explanation for this behavior is not available, it is believed that these bservations lend further evidence to support the hypothesis that the onset and duration of this condition are determined, at least in part, by developmental factors.

Mayo Clinic.

CONTROL OF AIR-BORNE INFECTIONS IN A NURSERY FOR YOUNG INFANTS

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IN 1927 there was an epidemic of enteritis at The Cradle, during which 27 deaths occurred among 80 infants with the disease. As a result of this epidemic, Dr. Gladys Dick introduced an individual aseptic nursery technic in 1929. From the introduction of this technic until April 1, 1946, there was no death due to enteritis contracted after admission. Furthermore, 3,780 infants were admitted, among whom were 52 with enteritis, 64 with impetigo and 10 with gonorrheal vaginitis, but no instance of cross infection from these infants occurred. The individual aseptic nursery technic has solved the problem of these hand-borne infections at The Cradle. Whether the same results can be obtained in a nursery for newborn infants is an open question; the traffic between mother and infant adds potential sources of infection to the nursery for newborn infants which are not present at The Cradle.

The elimination of direct and indirect contact had not solved the problem of air-borne infections.[1] In spite of the technic described, cross infections of the respiratory tract among the infants continued to occur, the only remaining vector being the air. There is ample evidence that intramural air is polluted with organisms from the nasopharynx of the human occupants, especially in wards for diseases of the respiratory tract. Sneezing, coughing and talking are accompanied with the constant escape of bacteria-laden droplets from the nose and mouth, a fact dramatically illustrated by Jennison's high speed photographs and by innumerable bacteriologic investigations. The smaller droplets, according to Wells,[1a] dry almost immediately on release and may float in the air for long periods, carrying pathogenic micro-organisms over long distances. The larger droplets by their gravity are rapidly removed from the air to settle on floors, bedclothes and other equipment, after

1. Sauer, L. W., and McDonald, J. J.: A Midsummer Respiratory Infection in an Aseptically Conducted Adoption Nursery, J. Pediat. **14**:304 (March) 1939; correction, ibid. **14**:557 (April) 1939.

1a. Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107**:1698 (Nov. 21) 1936. Wells, W. F.; Wells, M. W., and Mudd, S.: Infection of Air: Bacteriologic and Epidemiologic Factors, Am. J. Pub. Health **29**:863 (Aug.) 1939.

which they evaporate. It is well known that for weeks many pathogenic bacteria remain alive and infectious in floor dust and on blankets. With sweeping, bed making and other activities, the infected dust particles are released into the air and become a source of infection. According to recent investigations, the dust-borne bacteria play a major role in the spread of infections through the air. Observations at The Cradle have revealed that such activities as feeding and diapering the infant cause a considerable increase in the bacterial content of the air in the infants' cubicles (table 1).

The purpose of The Cradle's new building, erected in 1939, was to investigate certain methods of controlling these air-borne infections. The principles investigated up to the present time are air conditioning, germicidal lights, mechanical barriers and face masks. Other methods, such as sterilization of the air with germicidal vapor and "treatment" of blankets and floors with oil to reduce the hazard of bacteria carried

TABLE 1.—*Influence of Activity of Nurse on Number of Colonies per Ten Cubic Feet of Air in a Closed Air-Conditioned Cubicle* *

	No. of Colonies
No nurse in cubicle for 1 hr.	29
Nurse in cubicle feeding infant for 10 min.	119
No nurse in cubicle for 1 hr.	9
Nurse in cubicle diapering infant for 10 min.	209
No nurse in cubicle for 1 hr.	21
Nurse in cubicle motionless for 10 min.	47
No nurse in cubicle for 1 hr.	17

Ten minute samples were taken by the air centrifuge method.

in dust have not yet been included. A preliminary report on the results obtained with air conditioning, germicidal lamps and mechanical barriers, covering the period from 1939 to 1941, has been published.[2] It is the purpose of this paper to report on the results obtained from 1939 to 1946, with special reference to certain changes which have been made during recent years. The results will be presented for each principle in the following order: description of equipment, bacteriologic results and clinical results.

AIR CONDITIONING

There are three separate units of twelve cubicles each at The Cradle. All three units are equipped with air conditioning. Only outside air is used, with a complete exchange of inside for outside air at least every six minutes. A temperature of 75 F. and a relative humidity of 40 to 50 per cent are maintained. The bacteriologic results in a unit equipped with air conditioning as the only principle in the preven-

2. Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Control of Cross Infections of the Respiratory Tract, J. A. M. A. **118**:1271 (April 11) 1942.

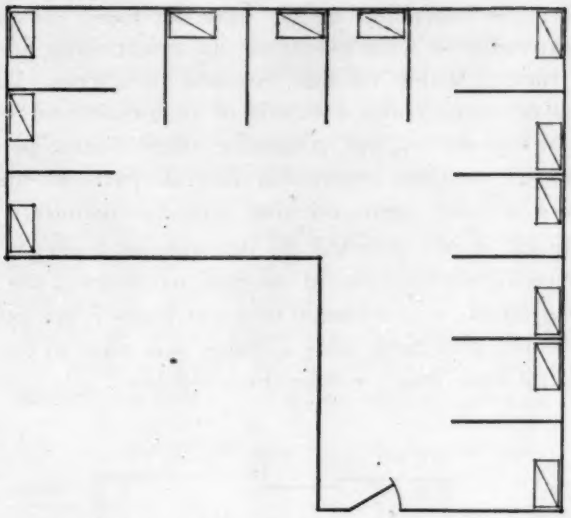

Fig. 1.—Diagram of control unit in which air conditioning alone was used to prevent air-borne infections.

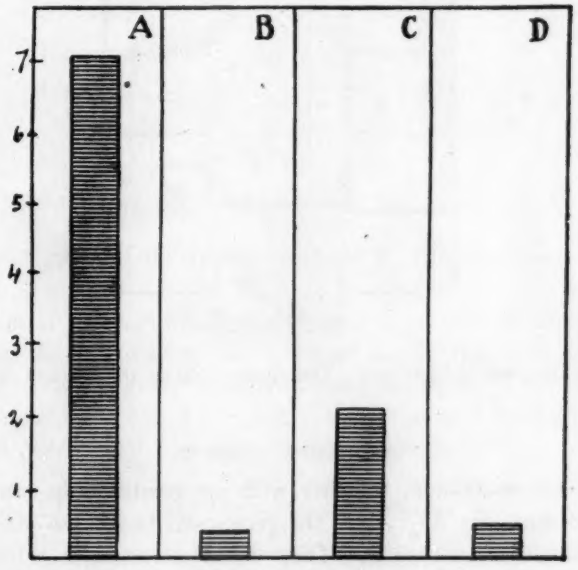

Fig. 2.—Chart showing incidence of cross infections of the respiratory tract in infants per year. Column *A* represents the incidence in a unit with air conditioning alone; column *B*, the incidence in a unit with air conditioning and germicidal light barriers; column *C*, the incidence in a unit with air conditioning and upper air irradiation, and Column *D*, the incidence in a unit with air conditioning and mechanical barriers.

tion of air-borne infections (fig. 1) were not found satisfactory. In order to determine to what extent the air conditioning prevented the spread of bacteria within the unit, Serratia marcescens (Bacillus prodigiosus) was sprayed into a cubicle or in the corridor of the unit. Plates were exposed for four successive fifteen minute periods. The results showed complete penetration into all parts of the unit and the presence of some organisms after forty-five minutes.

The clinical results reflected the bacteriologic findings. During a three year period the incidence of the cross infections of the respiratory tract among infants in the control unit was high—7 per year (fig. 2). For this reason, after three years a change was made in the equipment of the control unit, which will be discussed later.

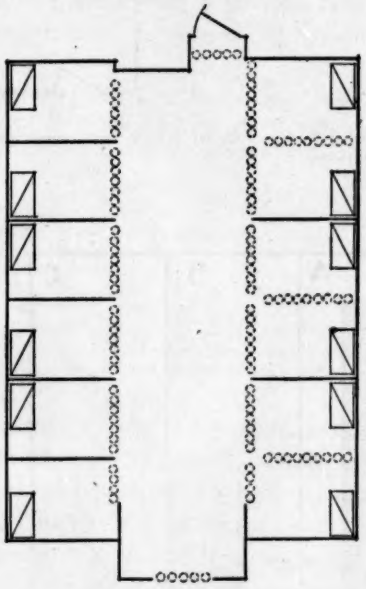

Fig. 3.—Diagram of light unit. The circles indicate the barriers of germicidal lights.

GERMICIDAL LIGHTS

Germicidal irradiation, together with air conditioning, was applied in a second unit (fig. 3). Here the germicidal lamps are placed above the open end of each cubicle. They throw a vertical curtain of light across its entrance. Six of the cubicles are separated with partitions from ceiling to floor; in the other six cubicles curtains of light alternate with solid partitions. The curtains of light are so designed that only a harmless fraction of the rays reaches the corner of the cubicle where the head of the infant is exposed. Nurses' eyes are protected with head shields and goggles.

The bacteriologic results with spraying of S. marcescens showed that there was no penetration from corridor to cubicle or from cubicle to corridor; the time of survival did not exceed fifteen minutes.

The clinical results in the light unit during a seven year period showed 0.3 cross infection of the respiratory tract in the infants per year, which is less than one twentieth the number in the control unit (fig. 2).

Because of the frequency of cross infections of the respiratory tract in the control unit during the first three years, germicidal lamps were also introduced in this unit. However, the type of installation was different. Instead of barrier irradiation, irradiation of the upper air was used from lamps mounted on the walls 7 feet (213 cm.) above the floor. The purpose was to determine whether this type of installa-

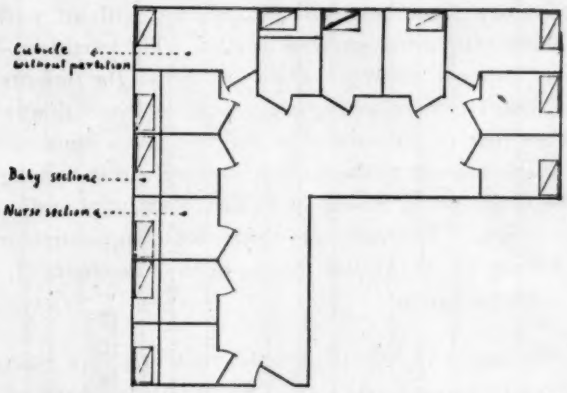

Fig. 4.—Diagram of unit in which mechanical barriers were used.

tion, which eliminates the harmful effects of direct irradiation, would be efficient.

The clinical results obtained during a four year period with air conditioning and irradiation of the upper air in this unit showed an appreciable reduction in the number of cross infections of the respiratory tract. The incidence was 2 per year, in contrast to 7 before the installation of the germicidal wall lamps (fig. 2).

MECHANICAL BARRIERS

Mechanical barriers in connection with air conditioning were used in a third unit (fig. 4). Each of these twelve cubicles is completely closed with a swinging door. In six of them a glass partition separates the inner section for the infant from the outer section for the nurse and supplies for the cubicle. Each section has an individual air supply and exhaust. The nurse enters the outer section, makes preparations

for the care of the infant, raises the glass window in the partition to shoulder level, attends the infant and then closes the window. The supply of air for the two sections is so arranged that the air pressure maintained in the infant's section is greater than that maintained in the nurse's section. Therefore, when the window is raised, air from the nurse's section cannot enter the infant's section. The six remaining cubicles are not divided into two sections.

Bacteriologic results with S. marcescens showed that there were no penetration from cubicle to cubicle, some penetration from cubicle to unit corridor and slight penetration from unit corridor to cubicle.

The clinical results were almost as satisfactory as those obtained in the light unit: 0.4 cross infection of the respiratory tract per year during a seven year period (fig. 2).

Since there was no difference in the occurrence of cross infections of the respiratory tract between the cubicles without partitions and those with them, they were removed in 1945. The partitions had proved advantageous in one respect. They protected the infants from the noise of the unit, thus increasing their sleeping time almost two hours each day over that of the infants in the two units with open cubicles. However, in other respects the partitions were a disadvantage. Infants could not be observed as closely as in the other units and could not be heard when crying. The care was somewhat complicated, and in some infants a slowing of the mental development was observed, apparently due to lack of stimulation.

SUMMARY OF RESULTS WITH APPLICATION OF AIR CONDITIONING, GERMICIDAL LIGHTS AND MECHANICAL BARRIERS

The incidence of cross infections of the respiratory tract in infants in the units per year was as follows:

	No. of Infections
Unit with air conditioning	7
Unit with air conditioning and germicidal light barriers	0.3
Unit with air conditioning and upper air irradiation	2
Unit with air conditioning and mechanical barriers	0.4

This distribution is all the more significant because the number of primary infections of the respiratory tract (those of nurses on duty and of infants admitted) was about the same in all the units (fig. 5).

FACE MASKS

Ventilation in connection with closed cubicles or with sterilization of the air with germicidal lamps minimized the spread of infections of the respiratory tract from cubicle to cubicle. But there remained another source of infection which could not be eliminated with the

devices described: the direct expulsion of organisms from the nasopharynx of the nurse to the infant while she attended the infant in the cubicle. In order to protect the infant from this source of infection, face masks are worn by all nurses and other attendants at The Cradle. The mask is supposed to act as a mechanical barrier, trapping the infected material at the source. While the use of face masks in operating rooms and in wards for contagious diseases is a generally accepted procedure, the question whether masks should be worn in infant nurseries does not seem to be entirely settled. The reason for this uncertainty is probably that no observations are available which allow valid conclusions. It seemed worth while to include the old problem of the masks in our investigations.

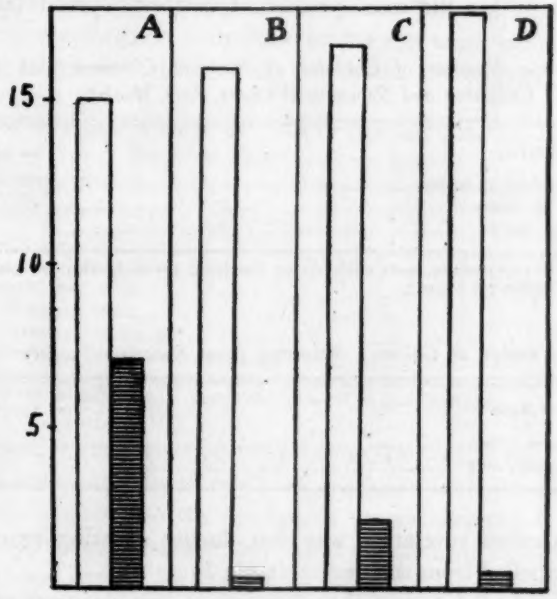

Fig. 5.—Chart showing comparative incidence per year of primary infections of the respiratory tract (white columns) among nurses on duty and infants admitted with colds and incidence of cross infections of the respiratory tract (black columns) in infants. The columns in section *A* represent the incidence in a unit with air conditioning alone; in section *B*, the incidence in a unit with air conditioning and germicidal light barriers; in section *C*, the incidence in a unit with air conditioning and germicidal upper air irradiation, and in section *D*, the incidence in a unit with air conditioning and mechanical barriers.

Face masks are worn by persons who are or who may be a source of infection and by persons who are exposed to infection. The first group includes attendants in operating rooms and in nurseries; the second, the personnel in wards for contagious diseases. In the first group, the mask is placed over the mouth and nose of the infector and is exposed to the force with which the droplets are propelled against

the mask; in the second group, the mask is at a greater distance from the source of infection and is not exposed to forceful currents. The masks worn by infectors or potential infectors must be much more efficient than the masks worn by exposed persons; this applies to the mask worn by attendants in nurseries.

The efficiency of face masks was extensively studied by means of several procedures: (1) atomizing bacterial suspensions on the mask, which was tied over a culture dish; (2) pulling a suspension of bacteria through the mask with suction, and (3) talking, coughing and sneezing through the mask. Only the last procedure simulates the actual conditions of use.

The most significant result of all investigations was that sneezing is the activity by far the most prolific of bacterial spread (table 2).

TABLE 2.—*Average Number of Colonies of Bacteria Obtained with Counting, Coughing and Sneezing Without Face Mask* *

Activity	No. of Colonies
Counting (aloud) (1 to 50)	25
Coughing, 10 times	22
Sneezing, 10 times	182

* Bacteria, in 20 experiments, were collected by the plate method, with the plate vertical at a distance of 7 inches (17.7 cm.).

TABLE 3.—*Number of Colonies Resulting from Sneezing Twenty Times*

Position of Mask	No. of Colonies
Covering nose only	736
Covering mouth only	34

Another unexpected revelation was that during sneezing most of the bacteria are expelled from the mouth (table 3).

Sneezing was used to test the efficiency of various types of masks. The procedure applied in the beginning was sneezing against vertical or horizontal plates, which were placed at various distances from the person who was sneezing. The results obtained with this method were not conclusive, since temperature, humidity and air currents, which may influence the growth of bacteria considerably, were not controlled. Furthermore, the sneezing against plates does not reflect the natural condition; it is not probable that the nurse would sneeze directly against the baby.

In order to work under controlled conditions and to obtain more complete data on the bacterial contamination of an enclosed space, I carried out the sneezing experiments in a closed air-conditioned cubicle and collected the bacteria with either the Wells air centrifuge or the plate method, the plates being placed at various heights.

Tests were made with the two main types of masks: the filtering and the deflecting type. The filtering masks included a mask of two layers of ordinary gauze and a commercial gauze-covered flannel filter mask, with a flexible metal strip across the top which could be molded snugly to the contour of the nose and cheeks and which kept glasses from fogging.[3] The deflecting types included a commercial mask made from pressed paper and a cellophane-gauze mask, as recommended by Blatt and Dale.[4] In the latter mask a piece of moisture-proof cellophane is sewed between two layers of 32 to 30 gauze. The upper and lower edges of the mask fit firmly against the face, while the center and sides are held away. A free breathing space is thus established, and the expired air is directed laterally and to the rear. A fifth mask investigated was a commercial type made of tissue-thin vegetable fiber.

The results obtained with these masks and when no mask was used (table 4) showed that three of the masks investigated were almost

TABLE 4.—*Average Number of Colonies Obtained from Sneezing Twenty Times in Air-Conditioned Cubicle* *

Type of Mask	No. of Colonies
Without mask	780
Gauze mask (2 layers)	183
Vegetable fiber mask	76
Pressed paper mask	46
Cellophane—gauze mask	46
Gauze-covered flannel filter mask	39

* Bacteria, in 60 experiments, were collected by the plate method.

equally effective: the gauze-covered flannel filter mask, the pressed paper mask and cellophane-gauze mask. Experience with the two deflecting masks does not confirm the opinion of several investigators that such masks are inefficient because they allow exhaled air to escape laterally to the rear and help in the contamination of the air of the room. However, the deflecting masks, especially when worn by a person with a cold, have a distinctive disadvantage. The mucus discharged from the nose and throat is not absorbed, as with a filtering mask, but accumulates on the inner surface of the mask and gradually produces an unpleasant and dangerous drop of the accumulated material from the area of the nose down to the mouth and chin. It is for this reason that the flannel filter mask seems preferable, in spite of the fact that this mask, especially when worn by a person with a cold, produces a moist chamber over the face which is uncomfortable during hot weather.

3. McKhann, C. F.; Steeger, A., and Long, A. P.: Hospital Infections, Am. J. Dis. Child. **55**:579 (March) 1938.

4. Blatt, M. L., and Dale, M. L.: A Bacteriological Study of the Efficiency of Face Masks, Surg., Gynec. & Obst. **57**:363 (Sept.) 1933.

The bacteriologic results were not conclusive. They had to be substantiated by clinical tests. A comparison of a nursery unit in which masks are worn with a unit in which no masks are worn under otherwise equivalent conditions would have been the decisive test. Such a study could not be found in the literature.

In our clinical investigations we approached the problem from another angle. Generally, a nurse with a cold is immediately taken off duty in nurseries. However desirable this policy may be, the practice offers many obstacles. The nurse does not always report her condition immediately, and in certain seasons there are so many nurses with colds that it is impossible to take them off duty. In view of this situation, which has been aggravated by the shortage of nurses, during the last seven years, we have permitted nurses with colds to remain on duty, provided their general condition allowed it. In this seven year period there were 245 infections of the respiratory tract in nurses who remained on duty during their infections. In 236 instances the nurse was the only source of infection, no infant in the unit having a cold at the same time. In only 9 of the 236 cases did a cross infection occur from nurse to infant. Since the nurses come in close contact with the infants, it is striking that the transmission of infections of the respiratory tract from nurse to infant was so infrequent. This low incidence indicates that the flannel and gauze mask worn by the nurses usually protects the infant.

A crucial experiment is being conducted now: a comparison in incidence of cross infection of the respiratory tract between a unit in which the nurses wear a flannel and gauze mask and a unit in which the nurses wear ordinary gauze masks or no masks.

CONCLUSIONS

Hand-borne cross infections have been eliminated at The Cradle through the application of an individual, aseptic nursery technic.

For the prevention of air-borne cross infections, air conditioning, germicidal lights, mechanical barriers and face masks have been in use at The Cradle, with the following results:

1. Air conditioning alone did not prevent the spread of cross infections of the respiratory tract.

2. Germicidal irradiation of the upper air and air conditioning reduced the number of cross infections of the respiratory tract.

3. Germicidal light barriers and air conditioning were efficient.

4. Mechanical barriers and air conditioning were efficient.

5. The flannel and gauze mask worn by all attendants seemed to be of value in preventing transmission of infections of the respiratory tract from nurse to infant.

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BOTULISM IN NEW MEXICO

Incidence Over Ten Years, with Report of Six Cases

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BOTULISM, fortunately, is relatively rare. A study of the cases reported in New Mexico from Jan. 1, 1936 to June 1, 1947 revealed fifteen outbreaks, with 44 persons affected and 30 deaths. These outbreaks occurred in twelve different counties in various parts of the state. Of the persons affected, 30 had eaten home-canned green chili; 2, hamburgers; 1, sardines; 2, home-canned green beans; 4, home-canned peaches, and 1, pimiento loaf, while for 4 the cause was not determined. Little has been written about the disease. Few textbooks devote more than half a page to it. The five volume work of von Pfaundler and Schlossman,[1] edited by Peterman, includes less than one-half page.

The organism causing botulism is Clostridium botulinum, types A and B, an anaerobic organism which grows only in a nonacid medium. It is readily destroyed by heat, by a 3 per cent solution of phenol or by light. It develops on both liquid and solid mediums, and the toxin is potent when injected subcutaneously or intravenously and when ingested orally. In Europe the bacillus has been found in meats, such as ham, sausage and salt fish. In the United States, it is detected oftener in the home-canned vegetables. The bacteria develops to varying degrees in different parts of the food. This uneven development perhaps explains why some persons are affected more severely than others who have eaten the same food. The only treatment of any value is the antitoxin, and the only patients benefited are those who get the antitoxin early. Unfortunately, many of them are ill for some time before they are seen; then it is too late to help them.

I am reporting cases of botulism in 4 persons of one family who had eaten some home-canned peaches at supper; 3 children and the grandmother were affected. The father, the mother and the baby of the family did not eat the fruit. The following morning, the child who had eaten the most of the peaches was extremely dizzy. He got up and dressed but decided he was too ill to go to school. The other 2 children, feeling only slightly dizzy, went on to school. One of them came home about 10 a.m., and the other at noon. Their only complaint was dizziness. They remained at home all afternoon and did not seem to feel ill. They had no pain and did not vomit, or have diarrhea.

1. von Pfaundler, M., and Schlossman, A. The Diseases of Children. A Work for the Practicing Physician, translated by M. G. Peterman. Philadelphia, J. B. Lippincott Company, 1935.

That night I was called to see them, about thirty hours after they had eaten the peaches. At that time the 3 children were so dizzy they could not sit up; they were cyanotic and had taken practically no food or liquids since they had eaten the fruit. While they were in no pain, they impressed me as being very sick. The grandmother was perfectly comfortable. After examination, hospitalization was believed to be the best course. On admission to the hospital, since the children were cyanotic, administration of oxygen to all 3 was started. Each child was given 1,000 cc. of 5 per cent dextrose and isotonic solution of sodium chloride intravenously to make up for the lack of fluid and food over the preceding thirty hours. So that none of the contaminated food might remain in the gastrointestinal tract, the stomachs of all 3 children were washed.

After telephone conferences with several of my colleagues, I decided that in all probability this condition was botulism. The state laboratory had a supply of botulism antitoxin; but by the time I obtained some of it the oldest boy had died. Twenty thousand units of the serum, which contained equal amounts of type A and type B botulism antitoxin, was given to the other children every four hours. Their temperatures were now subnormal, and they were extremely cyanotic, with labored breathing. They could answer questions, but only after being aroused. Neither of them had had a bowel movement from the time he ate the peaches, so enemas were given. After that treatment, rectal taps, 250 cc., were given every four hours. Thirty-six hours after ingestion of the fruit, both children showed almost complete paralysis of the throat and were unable to swallow. Fluids were given by gavage. They seemed to be in no particular pain but simply lacked ability to respond. Labored breathing persisted. They were given no sedatives, since they seemed to be in no pain and we were able to get antitoxin at once. The second boy died after forty-two hours. He had received 60,000 units of antitoxin. The youngest child, who had eaten less of the peaches and had stayed in school the longest, lived sixty-one hours. He was given 120,000 units of antitoxin before his death.

The grandmother visited the children the first day they were in the hospital, which was 6 miles (9.7 Km.) from their home. At that time she felt well. That night, forty-eight hours after eating the peaches, she began to be dizzy and complained of shortness of breath. She gradually became stuporous and could not respond well to questions. She was given stimulants and antitoxin, but to no avail.

An autopsy was performed on the boy who died first, but permission to examine the brain was not given. The autopsy showed nothing notable. The heart, lungs and liver were normal. The stomach and the intestine were seemingly normal, as were the kidneys and the spleen. This unremarkable autopsy is in keeping with what is expected when a healthy child is infected with botulinus toxin. According to the textbooks, the disease affects only the nerve tissues. This autopsy at least showed that botulism, and no other condition, caused death. The jar that held the peaches had been emptied and washed. However, I took it to the laboratory, and there the Cl. botulinum type A was discovered, which proved the case. The mother in her grief emptied every jar of peaches on the place, so that we had no chance to study any of the fruit itself. I am unable to find a report of any other case in which peaches were the source of the disease. The fruit is usually slightly acid. Cl. botulinum is supposedly unable to live in an acid medium. However, it is claimed that overripe peaches may lose their acidity; perhaps such a loss occurred in this instance.

Through the aid of Dr. L. G. Rice Jr., I wish to report 2 cases which occurred shortly after these 4

Two girls in a boarding school received a box from home which contained, among other things, a jar of canned green chili. With friends, they opened the box in their room. The chili when opened looked all right. Three girls each took a small taste but no more. Two of them, however, ate large portions of it. The next morning they did not feel well. The incident was reported to the superintendent of the school, and he hurried the girls to the hospital because of the recent occurrence of the aforementioned cases. Dr. Rice asked me to see these children, and we decided that they had botulism. Administration of antitoxin was started only fifteen hours after the girls ate the chili. They were given 20,000 units every four hours until the symptoms cleared. One of them was ill only two days, but the other, who had seemed sicker at the start, was not well for several days. The 1 who first recovered received 120,000 units, while the antitoxin was continued for the other until she received 250,000 units. The green chili was examined, and it was found to contain Cl. botulinum type A, which proved the cases.

I am glad to be able to add these 2 cases, as they emphasize an important fact. In the first 4 cases administration of the antitoxin was begun thirty-six hours after the children ate the contaminated food, and they all died. Antitoxin was given them in small amounts as long as they lived. However, the 2 patients of Dr. Rice received the first antitoxin only fifteen hours after eating the contaminated food, and they made a complete recovery. This report demonstrates that all the patients with botulism who are seen early have a chance to recover.

221 West Central Avenue.

Case Report

PROGRESSIVE LIPODYSTROPHY
ETIOLOGIC ASPECTS AND REPORT OF A CASE

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PROGRESSIVE lipodystrophy is characterized by a gradual loss of subcutaneous fat, involving usually the head, neck, shoulder girdle and upper extremities without a concomitant loss of fat deposits from other regions of the body. It occurs oftener in girls and classically has its onset between the ages of 6 and 12 years. The dystrophy progresses slowly over a number of years until nothing remains of the original fat deposits in the affected areas.

Other types of this disease, however, have been described, such as involvement of the lower extremities alone (Bigler [1]) or of all four extremities (Patton [2]). Progressive lipodystrophy of the face alone was reported by Guralnick and Green,[3] while Karger [4] described a case of "mirror image" lipodystrophy, with complete loss of cubcutaneous fat over the entire body except the face. Its occurrence in women of older age groups, especially at or soon after the menopause, was reported by Currier and Davis,[5] Ziegler,[6] Marañon and Blanco Soler [7] and Cohen and Eis.[8] Associated with the typical dystrophy affecting the face, neck and upper extremities there was often in these cases an increase in the deposition of fat on the lower extremities.

The search for the etiologic origin of the disorder has produced many theories, based on clinical signs and occasionally on laboratory data. Thus, a connection between lipodystrophy and the endocrine

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1. Bigler, J. A.: Loss of Subcutaneous Fat of the Lower Extremities (Lipodystrophy), J. A. M. A. **112**:627 (Feb. 18) 1939.

2. Patton, A. F.: Lipodystrophy with Involvement Restricted to the Four Extremities, Am. J. Dis. Child. **70**:31 (July) 1945.

3. Guralnick, R., and Green, H. Lipodystrophia Facialis, New England J Med. **220**:553, 1939.

4. Karger, cited by Schlau.[12]

5. Currier, F P., and Davis, D. B. Progressive Lipodystrophy Appearing at Menopause, Am. J. M. Sc. **179**:750, 1930.

6. Ziegler, L. H. Lipodystrophies: Report of Seven Cases, Brain **51**:147, 1928.

7 Marañon, G., and Blanco Soler, J.: Progressive Lipodystrophy and Hyperthyroidism, Endocrinology **10**:1, 1926.

8. Cohen, S. J., and Eis, B. M.: Lipodystrophy in Adults, Arch. Neurol. & Psychiat. **32**:184 (July) 1934.

system was suggested by Ziegler,[6] Kelin,[9] Currier and Davis,[5] Frazier,[10] Klein [11] and Schlau.[12] Action of the thyroid gland on the neurovegetative system was suggested by Marañon and Blanco Soler.[7] A neurotrophic disorder was considered by Klein,[11] Christiansen [13] and Marburg.[14] A general fault of fat metabolism was claimed by Harris and Reiser.[15] Encephalitic changes secondary to infectious or toxic damage to the brain were proposed as an etiologic basis by Wartenberg.[16]

It will be readily recognized that the aforementioned theories have not materially improved understanding of the etiology of progressive lipodystrophy. There are in the literature, however, several reports which may help in forming a conception of the etiologic source of this disease. These reports deal with congenital and hereditary changes in the anlage of the mesenchyme. Since subcutaneous tissue is derived from the mesenchyme, it has, in my opinion, an important bearing on the causation of this disease.

Frank [17] reported the case of an 11 year old girl who showed progressive lipodystrophy of the face, neck and shoulders with increased deposits of fat on the lower extremities, beginning at the age of 6 years. She had a systolic heart murmur, maximal in the midsternal line at the level of the second interspace, and an increased pulmonary second sound. The joint ligaments of her extremities were remarkably loose, allowing hyperextension. There was an increased tendency to bleeding of the subcutaneous blood vessels. The scleras were blue-gray. The reaction to the capillary permeability test was strongly positive. She had twice fractured her legs after minor trauma. In composing a chart of the pedigree, the author found that blue scleras, fragilitas ossium, progressive lipodystrophy, deafness, looseness of the ligaments and diseases of the circulatory system occurred in a significant number of members of the family throughout three generations.

Frank assumed as the basic cause of these abnormalities a poor development of the mesenchyme. Since subcutaneous tissues, skeletal structures, the circulatory system, involuntary musculature, ligaments, tendons and lymphoid tissue all develop from mesenchyme, he explained the occurrence of progressive lipodystrophy in his patient as an expres-

9. Kelin, cited by Currier and Davis.[5]

10. Frazier, C. H.: Pituitary Cachexia, Arch. Neurol. & Psychiat. **21**:1 (Jan.) 1929.

11. Klein, cited by Currier and Davis.[5]

12. Schlau, H.: Lipodystrophie, Abderhalden-Reaktion und diencephal-genitales System, Klin. Wchnschr. **8**:1031, 1929.

13. Christiansen, V.: Lipodystrophie progressiva, Rev. neurol. **38**:747, 1922.

14. Marburg, O.: Zur Frage der Lipodystrophia progressiva, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **30**:1, 1927.

15. Harris, J. S., and Reiser, R.: Lipodystrophy: Report of a Case with Metabolic Studies, Am. J. Dis. Child. **59**:143 (Jan.) 1940.

16. Wartenberg, cited by Wolff, H. G., and Ehrenclou, A. H.: Trophic Disorders of Central Origin: Report of a Case of Progressive Facial Hemiatrophy Associated with a Lipodystrophy and Other Metabolic Derangements, J. A. M. A. **88**:991 (March 26) 1927.

17. Frank, E. S.: Lipodystrophia progressiva und Osteopsathyrosis infantilis, Ztschr. f. Kinderh. **36**:229, 1923.

sion of a deranged mesenchymal development. He concluded, further, that such a derangement occurs in early embryonic life and may become hereditary.

Van Leeuwen [18] reported a family in which the following characteristics were inherited through several generations. mental debility, small stature, otosclerosis, multiple cysts of bone, progressive lipodystrophy, deficient pneumatization of the maxilla, infantile uterus and excessive growth of hair on the body and face. He described 3 sisters in this family, each of whom showed progressive lipodystrophy of the face, neck and arms, starting at about 6 years of age, and otosclerosis, multiple cysts of bone and mental debility. He concluded that this syndrome was due to a hereditary change in the germ plasm. Bauer and Stein [19] observed that hereditary deafness and otosclerosis, as well as labyrinthine deafness, are consequences of a constitutional inferiority of the auditory apparatus. Since such otologic defects occur in conjunction with progressive lipodystrophy (van Leeuwen [18]), it is inferred that the latter condition has a similar basis.

Bauer [20] described a case of progressive lipodystrophy with occurrence of a skeleton-like face in several members of the same family.

Aschner,[21] as a result of her studies of the Laurence-Moon-Biedl syndrome, stated that this condition is inherited and that there must exist pathologic genes linked to a normal genotype (Bauer). Deposition of fat, a pronounced feature in this syndrome, must have a representation in the gene pattern. Furthermore, according to Aschner, it is not required by the laws of heredity that all the various anomalies belonging to the syndrome be present in one patient.

Brennemann [22] cited a case of progressive lipodystrophy occurring in conjunction with osteogenesis imperfecta.

REPORT OF CASE

D. C., a 9 year old white boy, was referred to the Boston Floating Hospital for study because of increasing thinness of his face and vague abdominal pain.

Present Illness.—When he was 6 years of age, it was noticed that his face assumed a drawn look. This change was gradual but progressive. Since the onset, deep circumoral creases had developed, which were especially prominent on smiling. The cheeks had hollowed, producing a facial appearance suggesting serious illness. The mother noticed that the thinness was present only in the face and that the rest of the body remained well developed. Since the onset of his illness, the patient had been gaining almost 3 pounds (1.3 Kg.) per year. Six months before admission to the hospital he began to complain of pain in the left

18. van Leeuwen, H. C.: Ueber familiäres Vorkommen von Lipodystrophia progressiva zusammen mit Otosklerose, Knochencysten und geistiger Debilität, Ztschr. f. klin. Med. **123**:534, 1933.

19. Bauer, J., and Stein, C.: Vererbung und Konstitution bei Ohrenkrankheiten: Beiträge zur klinischen Konstitutionspathologie, Ztschr. f. Konstitutionslehre **10**: 483, 1925.

20. Bauer, cited by van Leeuwen.[18]

21. Aschner, B.: Zur Erbbiologie des Skelettsystems: Beiträge zur klinischen Konstitutionspathologie, Ztschr. f. Konstitutionslehre **14**:129, 1929.

22. Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W F Prior Company, Inc., 1944, vol. 1, chap. 41, p. 2.

subcostal area. This pain occurred about once every three weeks and lasted a few hours. It was frequently present at night and interfered with sleep. Whereas he used to void three or four times a day, he began to void five or six times during the day and twice at night. Beginning three weeks before his admission, he noticed a burning sensation on voiding and had profuse night sweats. The abdominal pain had become severer and continued for longer periods.

Past History.—During the first two or three months of life, a peculiarly hoarse cry was observed. A physician consulted at that time made a diagnosis of infantile larynx. Otherwise, the past history was noncontributory. The prenatal, natal and postnatal course was uneventful, and his growth and development were progressive and normal.

Family History.—The mother was 28 years of age. A tuberculous cervical lymph node was removed from her neck when she was 10 years of age. She had never had evidence of tuberculous infection elsewhere. The father, a salesman, aged 42, was in good health. One male sibling, 10 years of age, was entirely well. There had been several cases of tuberculosis in the families of both the mother and the father. An uncle of the patient, who died of pulmonary tuberculosis one year before, had been in contact with the patient for at least two weeks during the active phase of the disease. Regular roentgenographic examinations of the patient and of his family had shown no evidence of active tuberculosis. The brother of the patient's mother had a remarkably thin face, which had its onset at the age of about 8 years and persisted. The rest of his body remained well developed. The cause was never determined, in spite of frequent consultations with physicians. He had never had tuberculosis, and his health was excellent.

Physical Examination.—The boy was well developed and well nourished, and in no acute distress. The skin was sallow. The subcutaneous tissue was well developed everywhere except in the face, where apparently it was entirely absent. The cheeks were hollow, and the skeletal structure of the face was prominent. There were deep circumoral creases and prominent nasolabial folds. The face looked much older than the rest of the body, and one gained the impression of constant worry. The eyes were large and sunken. Examination showed that the eyes, ears, nose and mouth were normal. The thyroid gland was not enlarged. Examination of the lungs revealed nothing abnormal. The heart was not enlarged; its rate and rhythm were normal. There was a blowing systolic murmur in the pulmonic area, which was unaffected by position or exercise. The abdomen was soft. The liver was palpable just below the right costal margin. The spleen was not palpable. There was no costovertebral tenderness. However, definite localized tenderness was elicited on deep palpation in the left lower abdominal quadrant about midway between the umbilicus and the symphysis pubis. There was only a slight increase of muscular spasm in this area. The genitalia were normally developed. The extremities were normal, and the reflexes were physiologic. Throughout the examination the patient was cooperative but abnormally apprehensive. He had a precocious way of advancing questions concerning his medical care and treatment in the hospital. He seemed to be deeply worried and perspired profusely.

Laboratory Data.—Urinalyses on admission and subsequently gave results within normal limits. Examination of the blood on admission revealed 87 per cent hemoglobin, 5,000,000 red blood cells and 13,600 white blood cells per cubic millimeter, with a differential count of 32 per cent polymorphonuclear leukocytes, 10 per cent band forms, 3 per cent metamyelocytes, 45 per cent lymphocytes, 4 per cent eosinophils, 1 per cent basophils and 5 per cent

monocytes. Culture of material from the throat yielded occasional colonies of a beta hemolytic streptococcus. The reaction to the micro-Hinton test for syphilis was negative. The reaction to the tuberculin test (intradermal) was negative in a dilution of 1:20,000 and positive in a dilution of 1:100. Roentgenographic examination of the chest showed no evidence of a tuberculous lesion in the pulmonary fields. The heart was within normal limits for size and shape. An intravenous pyelogram revealed that both kidneys were normal in size, shape and position. There was prompt excretion of well concentrated dye, outlining both renal pelves and calices in a satisfactory manner. The left renal pelvis was wider than the right, and there appeared to be a constriction of the left ureter near the ureteropelvic junction. This constriction seemed to interfere with normal excretion, for the left renal pelvis remained partially filled forty minutes after injection, with the patient in the upright position. The right ureter was well outlined, whereas the left ureter showed only a few droplets of dye. The bladder appeared

Fig. 1.—Progressive lipodystrophy in a boy 9 years of age. The subcutaneous fat of the face is absent, resulting in prominence of the skeletal structure, nasolabial folds and a tired, worn expression.

normal. These findings were suggestive of an aberrant vessel at the left ureteropelvic junction. In addition, there was a spina bifida at the level of the fifth lumbar vertebra and partial sacralization of the left transverse process of this vertebra.

Operation and Postoperative Course.—On the fifteenth day in the hospital exploration through an incision in the left renal area revealed dilatation of the renal pelvis and the presence of three aberrant vessels, one of which produced the constriction indicated in the roentgenogram, while the others entered the lower pole in the left kidney. Each vessel was clamped, tied and severed. This procedure allowed the ureter to empty well. The patient was discharged on the fourteenth postoperative day, the twenty-ninth day of hospitalization.

Two and one-half months after discharge the patient was readmitted for follow-up study. During the interval he had gained 5 pounds (2.3 Kg.) and

had been asymptomatic, except for occasional mild headaches. He had had no urinary or abdominal complaints.

Subsequent Physical Examination.—The patient's condition was essentially the same as on his first admission. However, the loss of subcutaneous fat seemed to extend farther, involving the face, neck and shoulder girdle and being moderately evident over the arms. The superficial subclavicular veins were prominent. The cardiac signs were unchanged. There was no tenderness on abdominal palpation.

Laboratory Data.—Routine examination of the blood and urine gave results within normal limits. Determinations of the fasting blood sugar and of the blood sugar level three hours after taking food showed 91 mg. per hundred cubic centi-

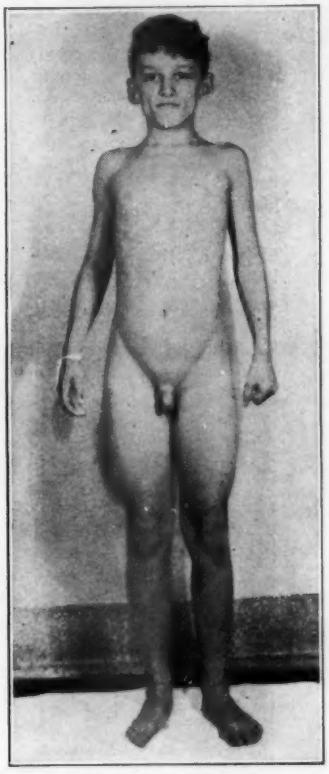

Fig. 2.—Photograph showing the pronounced contrast between absence of subcutaneous fat deposits on the face, neck and shoulder girdle and the presence of normal subcutaneous fat in the abdominal wall, arms and legs in a boy 9 years of age.

meters on each occasion. The basal metabolic rate was + 15 per cent in the first period and + 19 per cent in the second period. The value for the total fatty acids of the serum three and one-half hours after taking food was 345 mg. per hundred cubic centimeters. An intravenous pyelogram showed prompt excretion of well concentrated dye, outlining a slightly widened pelvis on either side. The left renal pelvis was still wider than the right. The obstruction at the left ureteropelvic junction was still present and seemed to interfere with drainage. However, the left ureter filled as well as the right.

COMMENT

This patient presented the classic picture of progressive lipodystrophy, as evidenced by the insidious onset, the slow progression and the absence of fat deposits over the face, neck and shoulder girdle, while the distribution of fat in other parts of the body was normal.

In addition, an intravenous pyelogram showed evidence of a congenital abnormality of the circulatory system, consisting of aberrant renal arteries, and the diagnosis was verified at operation. A persistent blowing systolic murmur, maximal in the second left interspace, pointed to a congenital heart murmur.

Fig. 3.—Photograph of uncle of D. C., aged 28, with thin, drawn face and well developed body.

Furthermore, roentgenographic evidence of congenital skeletal abnormalities was present in the form of a spina bifida involving the fifth lumbar vertebra and sacralization of the fifth lumbar transverse process with the left iliac crest.

A clinical history of progressive lipodystrophy in an uncle of the patient was obtained and was corroborated by a photograph.

In the absence of any other signs pointing to an organic system which could govern such a heterogeneous display of congenital abnormalities, strong evidence is offered in support of the view that the common denominator of all these defects is a congenital derangement

of the mesenchymal anlage. Since subcutaneous tissue is derived from mesenchyme, the occurrence of progressive lipodystrophy is merely an expression of such a derangement. It may occur alone or in conjunction with other congenital developmental defects affecting tissues derived from mesenchyme. Furthermore, there is evidence that such a deranged mesenchymal anlage may become hereditary and that in offspring it may give rise to one or more congenital abnormalities of structures derived from it.

SUMMARY

A case of progressive lipodystrophy is presented.

Emphasis is placed on the presence of multiple congenital abnormalities of tissues derived from mesenchyme and on the hereditary trend which this disease may assume.

32 Asylum Street.

Progress in Pediatrics

CONGENITAL ATRESIA OF THE SMALL INTESTINE IN THE NEWBORN

Report of Two Cases, With a Review of Successfully Treated Intrinsic Obstructions of the Small Bowel

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THE ONLY types of congenital abnormalities of the alimentary tract considered in this discussion are the complete intrinsic obstructions of the small bowel. Two general groups of such lesions exist: (1) one or more septums or diaphragms completely occluding the lumen and (2) narrowing of the intestinal diameter at one or more sites to the point of total obstruction. In the latter type, the proximal blind end of bowel may be completely separated from its distal counterpart, or the two ends may be joined with a solid cordlike structure, devoid of a lumen. Therefore, mesenteric defects may or may not occur.

The existence of these lesions has been recognized for more than two hundred years; the successful treatment of them has been known for less than forty years. There is now evident a gradual and encouraging increase in the number of patients whose defects have been successfully repaired. Yet reports of recoveries are unusual enough to be of interest.

Calder,[1] in 1733, described duodenal occlusion observed in a child at autopsy and thus made the pioneer contribution to the literature on congenital occlusion of the small bowel. In 1765, Daniel[2] reported a similarly affected infant, while in 1797 Osiander[3] discussed the case of a girl who died at the age of 5 days with complete obstruction of the lower portion of the ileum due to a diaphragm. In 1808, Aubéry[4] reported observation of atresia of both the duodenum and the common

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1. Calder, J.: Med. Essays & Obst. Soc. Edinburgh **1**:203, 1733.
2. Daniel, cited by DeSanctis and Craig.[13]
3. Osiander, F. B.: Neue Denkwurdigkeiten für Aerzte und Geburtshelfer Göttingen, J. G. Rosenbusch, 1797, pp. 179-180.
4. Aubéry: Ueber eine angeborne Trennung des Magens und Darmcanals in zwei Theile, Med.-Chir. Ztg. **4**:269, 1808.

bile duct in the same subject. In 1862, Hirschprung [5] collected 12 instances of congenital occlusion of the small bowel demonstrated at autopsy. In 1877, Theremin [6] contributed an excellent, and probably the first, review of the entire subject.

In 1889, congenital obstruction of the small bowel was first diagnosed in a living infant by Sutton,[7] who attempted the first operation for its correction. The lesion was an ileal atresia in a 48 hour old patient; an ileostomy was performed, but death occurred six hours later.

Discussions of observations at autopsy on these newborn infants were compiled by Cordes,[8] in 1901; Kuliga,[9] in 1903; Spriggs,[10] in 1912; Davis and Poynter,[11] in 1922, and Birgfeld,[12] in 1928. In 1929, DeSanctis and Craig [13] assembled reports of 129 recorded cases of duodenal occlusion. Later that year Kaldor [14] compiled 250 instances of duodenal atresia from the literature. More than three hundred other papers have dealt with the general topic of congenital obstruction of the alimentary canal.

INCIDENCE OF GASTROINTESTINAL ATRESIA

Statistics in the literature vary and suffer from inaccuracies in nomenclature. Considering atresias anywhere from the mouth down to, and including, the anus, Theremin,[6] in 1877, encountered 9 instances of atresia among 150,000 births in St. Petersburg (1:16,666), with but 2 such occurrences in 111,451 newborn Viennese infants (1:55,725).

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5. Hirschsprung: Der angeborne Verschluss der Speisröhe, mit einem Beitrage zur Kenntniss des angebornen Dünndarmverschlusses, Schmidt's Jahrb. **117-118**:310, 1863.

6. Theremin, E.: Ueber congenitale Occlusionen des Dünndarms, Deutsche Ztschr. f. Chir. **8**:34, 1877.

7. Sutton, J. B.: Imperforate Ileum, Am. J. M. Sc. **98**: 457, 1889.

8. Cordes, L.: Congenital Occlusion of the Duodenum, Arch. Pediat. **18**:401, 1901.

9. Kuliga, P.: Zur Genese der congenitalen Dünndarmstenosen und Atresien, Beitr. z. path. Anat. u. z. allg. Path. **33**:481, 1903.

10. Spriggs, N. I.: Congenital Intestinal Occlusion, Guy's Hosp. Rep. **66**:143, 1912.

11. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestines, with Report of a Case of Multiple Atresia of the Jejunum, Surg., Gynec. & Obst. **34**:35, 1922.

12. Birgfeld, E.: Zur kongenitalen Dünndarmatresie, Zentralbl. f. Chir. **55**. 1548, 1928.

13. DeSanctis, A. G., and Craig, J. D.: Congenital Duodenal Stenosis and Atresia, Am. J. Dis. Child. **37**:818 (April) 1929.

14. Kaldor, J. L.: Atresia of the Duodenum and Duodenal Diverticula, Ann. Surg. **89**:6, 1929.

Miller,[15] in 1894, found 36 cases of intestinal stenosis and atresia in 36,000 autopsies on children in Moscow (1:1,000). In 1916, Ernst[16] observed 2 cases of atresia of the small intestine among 41,000 births in Copenhagen, Denmark. Losee,[17] in 1927, encountered duodenal atresia in 2 cases while reviewing the records of 3,000 necropsies performed during a fifteen year period in New York city. He further mentioned the presence of 1 case of jejunal and 1 of ileal atresia, presumably in the same pathologic material. During the same period, approximately 70,000 newborn infants were under observation.

In attempting to limit statistics to incidence of the defect in the small intestine, we found that figures on relative distribution are more plentiful than those on absolute incidence. Cole[18] reported 2 instances of atresia of the small bowel (1 of the duodenal and 1 of the ileal type) among 6,300 births at Barnes Hospital, in St. Louis (1:3,150). Thorndike[19] estimated that 1 infant in every 30,000 had duodenal atresia. Lee[20] mentioned Krieg's compilation[20a] of 688,992 consecutive cases of newborn infants collected by Theremin, Thorndike, von Koós and DeSanctis and Craig, among which 31 instances of intrinsic intestinal deformities occurred (1:21,580). These lesions may not all be complete occlusions.

At the North Carolina Baptist Hospital and the Bowman Gray School of Medicine of Wake Forest College, during the five year period from Jan. 1, 1941 to Dec. 31, 1946, 5,439 living babies were born, 3,034 children (up to 13 years of age) were admitted to the department of pediatrics and 110 autopsies were performed on newborn infants (52 on stillborn infants and 58 on infants who died in the neonatal period). Among these subjects, intestinal atresia was encountered in the 2 instances here reported and in 1 other possible case in which death occurred and which is not reported because of insufficient data.

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15. Miller, cited by Davis and Poynter.[11]

16. Ernst, N. P. Congenital Atresia of the Duodenum Treated Successfully by Operation, Brit. M. J. **1**:644, 1916.

17 Losee, J. R.: Some Congenital Anomalies of the Gastro-Intestinal Tract, Bull. Lying-In Hosp., New York **13**:148, 1927.

18. Cole, W H.: Congenital Malformation of Intestinal Tract and Bile Ducts in Infancy and Childhood, Arch. Surg. **23**:820 (Nov.) 1931.

19. Thorndike, A.: Duodenal Atresia and Stenosis in Infancy, Boston M. & S. J. **196**:763, 1927.

20. Lee, W E., in discussion on Stetten, DeW.: Ann. Surg. **111**:583, April 1940.

20a. Krieg, E. G.: Duodenal Diaphragm, Ann. Surg. **106**:33, 1937.

Table 1 indicates the variation in statistics on the relative distribution of the sites of atresias of the small bowel. Ladd and Gross [21] mentioned a lower incidence of duodenal atresia (9.6 per cent) than did Forssner [22] (28.8 per cent), Davis and Poynter [11] (34.2 per cent), von Koós [23] (40 per cent) or Tandler [24] (37.5 per cent). On the other hand, Ladd and Gross [21] encountered a higher relative occurrence of atresia of the jejunoileum (76.8 per cent) than did Forssner (42.2 per cent).

OCCURRENCE OF MULTIPLE ATRESIAS

Ladd and Gross [21] observed multiple sites of obstruction in 5.7 per cent of 52 patients with atresia of the small bowel. Davis and Poynter [11] reported that 16.6 per cent of the 401 patients had multiple lesions.

TABLE 1.—*Sites of Intestinal Atresias Mentioned by Various Authors*

Location	Forssner [22]		Davis and Poynter [11]		Ladd and Gross [21]	
	No. of Cases	Per Cent of Cases	No. of Cases	Per Cent of Cases	No. of Cases	Per Cent of Cases
Duodenum	13	28.8	134	34.2	5	9.6
Jejunum			60	15.3	6	11.5
Ileum					34	65.3
Jejunoileum	19	42.2				
Ileum and cecum			101	25.7		
Ileocecal valve	8	17.7			2	3.8
Colon	5	11.0	39	8.1	2	3.8
Multiple			67	16.6	3	5.7
Total	45		401		52	

Richter [25] estimated the incidence of multiple atresia at 25 per cent. Multiple lesions of the small bowel were recorded by Baugher [26] (four sites); Arnheim [27] (two sites); Glover, Smith and Eitzen [28] (eight

21. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

22. Forssner, H.: Die angeborenen Darm- und Oesophagusatresien, Anat. Hefte, 1907, no. 34, p. 1.

23. von Koós, A.: Die kongenitalen Atresien des Zwölffingerdarmes, Jahrb. f. Kinderh. **93**:240, 1920.

24. Tandler, J.: Zur Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien, Morphol. Jahrb. **29**:187, 1900.

25. Richter, H. M., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 3, p. 512.

26. Baugher, A. H.: Congenital Atresia of the Small Intestine, Tr. Chicago Path. Soc. **9**:34, 1913.

27. Arnheim, E. E.: Congenital Ileal Atresia with Gangrene, Perforation and Peritonitis in a Newborn Infant: Staged Operations; Obstructive Resection, Ileocolostomy and Excision of Exteriorized Ileum, Am. J. Dis. Child. **69**:108 (Feb.) 1945.

28. Glover, D. M.; Smith, S., and Eitzen, O.: Multiple Atresia of the Small Intestine: Case Report, Ann. Surg. **116**:337, 1942.

TABLE 2.—*Cases of Complete Congenital Atresias of the Small Intestine Successfully Treated*

Reported by	Date of Operation	Site of Atresia	Single or Multiple	Age at Operation	Surgical Procedure
Fockens, 1911 [65]	11/14/1910	Junction middle and lower thirds of small intestine	Single	8 days	Side to side anastomosis
Ernst, 1916 [16]	11/30/1914	Duodenojejunal junction	Single	11 days	Anterior duodenojejunostomy
Porter, L., and Carter, W. E.: Management of the Sick Infant and Child, ed. 6, St. Louis, C. V. Mosby Company, 1942	1920	Duodenum	Single	4 days	Gastroenterostomy
Demmer, 1927 [66]	9/21/1921	Terminal ileum	Single	1 hour	Resected both stumps; side to side ileocolostomy
Richter, 1924 [26]	1924	Duodenojejunal junction	Single (volvulus of ileum)	4 days	Posterior gastroenterostomy; release of volvulus of ileum
Sweet and Robertson, 1927 [60]	9/30/1926	Duodenojejunal junction	Single	(1) 10 days (2) 32 days	(1) Anterior gastroenterostomy (2) Duodenojejunostomy
Rotter, J. W. N.: Deutsche Ztschr. f. Chir. **219**: 339, 1929	7/ 7/1928	Terminal ileum	Single (volvulus of small bowel)	1 day	Release of volvulus; resection of stumps; end to end anastomosis
Jones and Morton, 1938 [70]	5/ 5/1930 6/ 4/1932	Third part of duodenum Second part of duodenum	Single Single	4 days 14 days	Posterior gastroenterostomy Duodenotomy; removal of septum
Reisman, H. A.: J. Pediat. **10**: 622, 1937	8/12/1930	Midileum	Single	4 days	Ileosigmoidostomy
Carter, 1933 [71]	8/12/1930	Lower ileum	Single	(1) 4 days (2) 28 days	(1) Ileocolostomy with proximal tube ileostomy (2) Closure of tube ileostomy
Corkill and Corkill, 1934 [69]	9/11/1933	Midileum	Multiple	2 days	Side to side ileocolostomy with proximal tube ileostomy
Martin and Elkin, 1937 [73]	January 1935	Lower ileum	Single	(1) 3 days (2) 33 days	(1) Enterostomy (2) Resection of exteriorized segment and side to side anastomosis
Stetten, DeW.: Ann. Surg. **111**: 583, 1940	4/ 1/1938	Duodenojejunal junction	Single	3 days	Duodenojejunostomy
Feggetter, S.: Lancet **2**: 188, 1940	12/ 5/1939	Second part duodenum	Single	11 days	Posterior gastroenterostomy

Ladd and Gross, 1941 [21]	.....	Duodenum—1 case Jejunun—3 cases Ileum—3 cases	....	....	Gastrojejunostomy Jejunoileostomy (1 with resection) 1: ileostomy with ileoileostomy; 2: ileocolostomy or ileoileostomy
Miller and others, 1943 [78]	3/25/1941	Low ileum	Single	8 days	Side to side anastomosis with proximal catheter enterostomy
	1/13/1942	Low ileum	Single	5 days	Enteroenterostomy with proximal catheter enterostomy
Arnheim, 1945 [27]	4/ 9/1942	Upper and lower ileum	Multiple	(1) 26 hours (2) 60 hours (3) 65 days	(1) Ileostomy with exteriorization of proximal and distal ends of ileum (2) Side to side ileocolostomy (3) Resection of original ileostomy and a second atresia of ileum
Duncan and others, 1943 [66]	8/29/1942	Upper and lower jejunum	Multiple	36 hours	Resection of blind loop and stenotic distal stump, side to side anastomosis
Donovan [63]	12/ 9/1942 10/18/1944	Second part duodenum Ileum	Single Single	10 days 2 days	Duodenojejunostomy Jejunoileostomy
Ward, C. S., Jr., and Cooper, F. W., Jr.: Ann. Surg. **117**: 718, 1943	1943	Second part duodenum	Single	5 days	End to side duodenoduodenostomy
Erb and Smith, 1944 [29]	1943 (?)	Upper and lower jejunum	Multiple	64 hours	Side to side anastomosis
Walkling, A. A.: Personal communication to the authors	4/ 5/1944	Ileum	Single	72 hours	Resection distal ileum; side to side ileo-ascending colostomy
Neuhauser, 1944 [59]	1944 (?)	Jejunum	Single	3 days	Side to side anastomosis
Sumner, W. C., and Morris, K. A.: Am. J. Surg. **68**: 120, 1945	9/16/1943	Second part duodenum	Single	6 days	Posterior gastrojejunostomy
Biggs, A. D., and Pontius, G. V.: Am. J. Dis. Child. **70**: 254 (Oct.) 1945	.....	Third part of duodenum	Single	72 hours	Duodenojejunostomy
O'Neill and others, 1947, present report....	8/ 4/1945	Ileum	Single	30 hours	Resection both stumps and side to side ileoileostomy
	11/10/1946	Second part of duodenum	Single	9 days	Duodenojejunostomy

sites); Erb and Smith [29] (four sites) and others (table 2).

Various combinations of stenoses and atresias of various parts of the alimentary canal were discussed by Loitman [30]; Ladd, Donovan and Gross,[31] and Little and Helmholz.[32]

Such statistics are of more than academic importance, for they serve as a constant warning to the surgeon that the observation of one site of atresia should never so preoccupy his interest that he neglects to examine the entire length of the large and small bowel. The danger from other unsought and unseen obstructions is far greater than the risk of the search. The fact that 4 infants with multiple atresias of the small bowel have been successfully treated is encouraging.

INCIDENCE OF ASSOCIATED DEFORMITIES OF OTHER ORGANS

Associated congenital anomalies of other organs appear to be unusual, the estimate of incidence varying from 0.5 per cent, reported by Davis and Poynter,[11] to 5 to 7 per cent reported by DeSanctis and Craig.[13] Sporadic references are found to such associated defects as clubfoot, hydrorachis, situs transversus, absence of omentum, mongolism, patent foramen ovale and absence of various organs.

FAMILIAL TENDENCY TO INTESTINAL ATRESIAS

Occurrence of atresias in siblings is apparently unusual. The "probable" occurrence of several cases in one family was discussed by Rogers [33] and by Farr and Fries.[34] Denny and Sloan [35] described the cases of identical twin girls, 1 with multiple atresias of the small bowel and the other with a huge defect of the anterior abdominal wall, associated with faulty rotation of the intestine and multiple atresias of the large bowel.

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29 Erb, W. H., and Smith, D. C.: Atresia of Small Intestine, Ann. Surg. **120**:66, 1944.

30. Loitman, C.: Congenital Occlusion of the Intestine, with Report of Four Cases, Boston M. & S. J. **197**:21, 1927.

31 Ladd, W. E., Donovan, E. J., and Gross, R. E. Panel Discussion on Intestinal Obstruction in Infancy, J. Pediat. **21**:264, 1942.

32 Little, H. M., and Helmholz, H. F. Situs Transversus and Atresia of the Pylorus, Bull. Johns Hopkins Hosp. **16**:249, 1905.

33. Rogers, E. J. A.: Successful Operation for Intestinal Obstruction in an Infant Sixty-Four Hours Old, M. News **71**:435, 1897. This report is an engaging account of one of the earliest, if not the first, successfully treated infant with a complete obstruction of the small bowel, due to adhesive bands.

34. Farr, C. E., and Fries, M.: Congenital Occlusion of the Bowel, S. Clin. North America **5**:621, 1925.

35. Denny, E. S., and Sloan, L. H. Congenital Intestinal Malformation in Identical Twins, S. Clin. North America **12**:227, 1932.

ETIOLOGIC THEORIES

Many commendable discussions have appeared dealing with suggested causes of intrinsic atresia of the small bowel. The etiologic theories are simply enumerated in the following paragraphs, with some of their respective proponents:

1. Fetal peritonitis (Fiedler [36])
2. Congenital volvulus or adhesive bands causing strangulation (Gaertner,[37] Morley,[38] Clogg [39])
3. Atresia occurring at the site of an "embryonic event" (Sutton,[7] Anders [40])
4. Degeneration of mucosa from unknown factors (Marckwald [41])
5. Persistence of epithelial overgrowths (Forssner,[22] Ager [42])
6. Intussusception of a loop of intestine, with absorption of necrotic bowel (Braun,[43] Chiari [44])
7. Developmental anomalies of mesenteric vessels (Wyss,[45] Little and Helmholz [32])
8. Abnormalities in nerve supply (Fraser,[46] Smith [47])
9. Occlusion of mesenteric arteries by sclerosis, resulting in local degeneration of the mucosa (Davis and Poynter [11])
10. Intrauterine enteritis (Thorel [48])
11. Congenital syphilis (Holt and Howland [49])
12. Errors in intestinal rotation (Dott [50])

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36. Fiedler, A.: Fall von Atresie des Dünndarms, Arch. d. Heilk. **5**:78, 1864.
37. Gaertner, F.: Multiple Atresien und Stenosen des Darms bei einem neugeborenen Knaben, Jahrb. f. Kinderh. **20**:403, 1883.
38. Morley, J.: Congenital Occlusion of Ileum, Brit. J. Surg. **9**:103, 1921.
39. Clogg, H. S.: Congenital Intestinal Atresia, Lancet **2**:1770, 1904.
40. Anders, H. E.: Ueber die Entstehung der kongenitaler Dünndarmatresien besonders des Duodenums, Verhandl. d. deutsch. path. Gesellsch., 1923, p. 337.
41. Marckwald: Ein Fall von Atresia oesophagi, duodeni, recti congenita, München. med. Wchnschr. **41**:265, 1894.
42. Ager, L. C.: The Cause of Duodenal Atresia, Arch. Pediat. **27**:135, 1910.
43. Braun, H.: Ueber den angeborenen Verschluss des Dünndarms und seine operative Behandlung, Beitr. z. klin. Chir. **34**:993, 1902.
44. Chiari, H.: Ueber eine intrauterin entstandene und von Darmatresie gefolgte Intussusception des Ileums, Prag. med. Wchnschr. **13**:399, 1888.
45. Wyss, M. O.: Ueber congenitale Duodenal-Atresien, Beitr. z. klin. Chir. **26**:631, 1900.
46. Fraser, J.: Surgery of Childhood, New York, William Wood & Company, 1926, vol. 2.
47. Smith, G. K.: Congenital Intestinal Occlusion, with Report on Five Cases. M. J. Australia **2**:685, 1932.
48. Thorel, C.: Ein Fall von multiplen congenitalen Atresien des Dünndarms, München. med. Wchnschr. **46**:1902, 1899.
49. Holt, L. E., and Howland, J.: The Diseases of Infancy and Childhood, New York, D. Appleton & Company, 1916.
50. Dott, N. M.: Anomalies of Intestinal Rotation, Brit. J. Surg. **11**:251, 1923-1924.

13. Pressure from surrounding organs (Farr and Brunkow,[51] Cordes [8])

14. Excessive atrophy and involution of the vitelline duct, involving the intestine (Birnbaum [52])

15. Strangulation of a loop of bowel by an umbilical ring, due (1) to excessive traction by a persistent omphalomesenteric duct (Ahlfeld [53]) or (2) to overdevelopment of the cecum in the root of the umbilical cord, preventing its retraction into the abdomen and causing it to become pinched off (Seisser [54])

It seems unwise to attempt to ascribe all cases to one cause; rather, one should apply to a given cause that etiologic theory, or theories, which best explain the pathologic changes present.

DIAGNOSIS OF CONGENITAL OBSTRUCTION OF THE SMALL INTESTINE

Obviously, preoperative differentiation of intrinsic from extrinsic obstruction, of advanced stenosis from atresia, of low ileal from proximal colonic lesions, is of less practical importance than the demonstration that obstruction exists and the approximate location of the (most proximal) site of obstruction, when possible. The following symptoms are significant on localization:

Vomiting.—Usually starting within forty-eight hours of birth, vomiting is frequent, persistent and forceful and the vomitus may be bloody. Cowell [55] estimated that hematemesis occurs in 65 per cent of infants with atresias. The vomitus may or may not be bile stained, depending on the site of the obstruction and the presence or absence of deformities of the bile duct. All vomitus should be examined for bile and blood. In cases of low obstruction the vomitus may become fecal as the hours pass.

Scantiness or Absence of Stools.—The infant may pass nothing per rectum; a small meconium plug may be expelled, or, on digital rectal examination, the finger may be stained with meconium. The passage of meconium obviously does not rule out even a complete obstruction, for the material may have formed in the lumen of the bowel distal to the occlusion. The meconium may appear grossly normal, but examinations may reveal absence of bile, or a stained smear, prepared as described by Farber,[56] may demonstrate the absence of lanugo or of cornified epithelial cells.

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51. Farr, R. E., and Brunkow, C. W.: Congenital Abnormalities of the Intestine: Intestinal Aplasia; Atresia of Rectum and Anus Complicated by Rectovesical Fistula with Report of Cases, Arch. Surg. **11**:417 (Sept.) 1925.

52. Birnbaum, R. H.: A Clinical Manual of the Malformations and Congenital Diseases of the Foetus, translated by G. Blacker, London, J. & A. Churchill, 1912, p. 170.

53. Ahlfeld: Zur Aetiologie der Darmdefecte und der Atresia ani, Arch. f. Gynaek. **5**:230, 1873.

54. Seisser, F.: Ueber einem seltenen Fall von partiellem Darmdefekt, Centralbl. f. allg. Path. u. path. Anat. **34**:140, 1923.

55. Cowell, E. M.: Congenital Occlusion of the Duodenum, Quart. J. Med. **5**:401, 1911-1912.

56. Farber, S.: Congenital Atresia of the Alimentary Tract: Diagnosis by Microscopic Examination of Meconium, J. A. M. A. **100**:1753 (June 3) 1933.

Total absence of bile is presumptive evidence of a complete occlusion distal to the ampulla of Vater, although complete obstruction of bile ducts must be considered.

There is evidence (Cordes [8]) that the atretic lesion, although complete and distal to the second part of the duodenum, may have developed after delivery of bile into the bowel had begun. According to Kölliker,[57] a material similar to bile may occur in the intestine as early as the third month of gestation.

When preoperative studies reveal meconium free from bile, the bile ducts should be examined at the time of operation, even though the atresia of the bowel is distal to the ampulla of Vater, for obstruction of the bile ducts may be an associated lesion. The presence of bile in the meconium or vomitus is not an infallible guide to the site of the atretic lesion, for, as Cordes pointed out,[8] accessory bile ducts may deliver bile to an astonishing variety of locations in the bowel.

Farber [56] expressed the belief that absence of cornified epithelial cells in stained smears of meconium is proof of the existence of congenital atresia of the alimentary canal. Bryan,[58] however, stated the opinion that those elements in meconium which come from amniotic fluid make their appearance at about the fifth month of fetal life. Some embryologists are of the opinion that hairs are produced above the surface of the fetal skin at about the fifth month of gestation. Since Bryan [58] reported that in his case hairs were present in the ileum distal to the site of a complete ileal atresia, he expressed the opinion that an intestinal atresia can develop after the fifth month of fetal life. He stated that therefore absence of cornified epithelial cells and lanugo in the meconium of the newborn indicates a complete atresia which developed before the fifth month of fetal life.

Abdominal Distention.—Whether or not abdominal distention is present depends on the site of the obstruction and the time at which the patient is observed. If the obstruction is high, any distention present probably also will be high, owing to dilatation, and possibly some hypertrophy, of the stomach and duodenum. Many authors have discussed the contrast between the resiliency of a dilated duodenum and the relative hardness and smallness of the ovoid mass caused by hypertrophied pyloric muscle.

When the intestinal occlusion is low, diffuse abdominal distention is more likely to be present. In either high or low obstructions, outlines

57. Kölliker, in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2.

58. Bryan, R. C.: Congenital Occlusion of the Small Intestine, Am. J. Surg. 37:297, 1923.

of gastric and intestinal margins may be traced on the abdominal wall, with or without visible and audible peristalsis.

Changes Visible on Roentgenographic Examination.—A plain roentgenogram of the abdomen will often suffice to establish the diagnosis of obstruction by outlining the distended stomach or intestinal loops proximal to the atresia. The oral administration of barium sulfate to patients with suspected atresia is both condemned and condoned by various authors. If it is felt necessary to employ barium in making a study of these infants, a small amount should be used, and then only when there is good reason to feel that the lesion is high, so that the barium can be aspirated from the stomach and duodenum before celiotomy. The presence of intraperitoneal calcified shadows on the plain roentgenogram may furnish strong evidence that an obstructive lesion of the intestine exists.[59]

Loss of Weight or Failure to Gain Weight.—The severity of these signs, obviously the sequelae of persistent vomiting and poor absorption from the proximal segment of the intestine, is in direct proportion to the lapse of time between the onset of symptoms and the institution of treatment. High obstructions are usually characterized by more rapid loss of weight than low ones.

Dehydration and Acid-Base Imbalance.—Dehydration and acid-base imbalance, which are sequelae of loss of fluid and electrolyte from vomiting, must be studied and adequately treated before operation.

Comment.—In the differential diagnosis, the most important consideration is to distinguish between vomiting caused by alimentary abnormalities and vomiting caused by some other lesion, particularly intracranial hemorrhage or an infectious process. The signs of an infection will vary greatly with its nature and location. In newborn infants with intracranial bleeding, a history of birth trauma may be secured, cyanosis and anorexia are apt to occur (infants with intestinal anomalies usually take their feedings well), the vomiting is less likely to be related to feedings and other signs of neurologic disorders are usually present.

The possibility of intestinal obstructions must then be considered. Esophageal atresia, with or without tracheoesophageal fistula, usually results in cyanosis, excessive saliva in the mouth and immediate vomiting of fluid offered. A soft catheter, when introduced into the esophagus, will meet obstruction, and a plain roentgenogram reveals no air in the stomach unless a tracheoesophageal fistula exists.

Hypertrophic pyloric stenosis usually occurs in boys from 4 to 6 weeks of age; the vomitus is free from bile, and a pyloric tumor can be felt in almost all instances.

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59. Neuhauser, E. B. D.: The Roentgen Diagnosis of Fetal Meconium Peritonitis, Am. J. Roentgenol. **51**:421, 1944.

The presence of an imperforate anus or a rectal atresia may be confirmed by digital examination.

SURVIVAL TIME IN CASES OF UNTREATED ATRESIA

Davis and Poynter [11] stated that the interval of survival averages six days. Sweet and Robertson [60] observed an infant with atresia of the small bowel who lived more than three weeks, even though no oral feedings were retained and no parenteral feedings were given. Keith [61] mentioned a child with complete duodenal atresia who survived nine months. He felt that the infant absorbed sufficient nutrition from its stomach to maintain life for this period.

MORTALITY RATES FOLLOWING SURGICAL CORRECTION OF ATRESIA

In 1933, Ladd,[62] after reviewing 349 articles, collected reports of 8 successfully treated patients with intrinsic intestinal obstruction. No mention was made of the percentage rate of survival represented by these figures. In June 1941, Ladd and Gross [21] reported a series of 52 cases, and in this number there were 45 deaths and 7 recoveries, a mortality rate of 86.5 per cent. Donovan [63] operated on 9 infants for complete atresia of the small bowel, with 2 recoveries, a mortality rate of 77.7 per cent. Miller [64] reported that until 1918 only 2 successful results had been secured in treating intrinsic obstruction of the small bowel. By 1928 this number was raised to 9, and by 1938 the total reached 16.

CASES OF SUCCESSFULLY TREATED CONGENITAL ATRESIA OF THE SMALL INTESTINE

In this paper, an attempt has been made to record all the cases of successfully treated complete atresias of the small intestine, but in several instances it was impossible to determine the exact nature and completeness of a given occlusion. Thus, two series of cases of successfully treated obstructions of the small bowel have been compiled, one in which the diagnosis of complete atresia was definite, and the other in which complete atresia was probable but not certain. From this compilation, it is evident that since 1910, when Fockens [65] performed

60. Sweet, G. B., and Robertson, C.: A Case of Congenital Atresia of the Jejunum with Recovery, Arch. Dis. Childhood **2**:186, 1927.

61. Keith, A.: A Demonstration on Constrictions and Occlusions of the Alimentary Tract of Congenital or Obscure Origin, Brit. M. J. **1**:301, 1910.

62. Ladd, W. E.: Congenital Obstruction of the Small Intestine, J. A. M. A. **101**:1453 (Nov. 4) 1933.

63. Donovan, E. J.: Personal communication to the authors.

64. Miller, E. M.: Bowel Obstruction in the Newborn, Ann. Surg. **110**:587, 1939.

65. Fockens, P.: Ein operativ geheilter Fall von kongenitaler Dünndarmatresie, Zentralbl. f. Chir. **38**:532, 1911.

the first successful operation for atresia of the small bowel, there have been reported 34 instances of recovery following surgical repair of definitely demonstrated, complete atresia of the duodenum, jejunum or ileum. The 2 cases here described bring the total to 36.

In addition, descriptions have been collected of 13 cases of sucessful operation for obstructions which were probably, but not certainly, complete and intrinsic (table 3). The two series, including the cases here reported, bring the total to 49 cases. In many other cases similar lesions undoubtedly have been successfully treated, but either the cases have not been reported or the reports have not been encountered.

A review of the cases of obstruction which were successfully treated presents interesting topics for discussion.

Sex Distribution.—There is an approximately equal distribution between the sexes.

Optimum Time of Operation.—The age at the time of operation in the cases of successfully treated atresias varied from 1 hour to 11 days. In the case in which operation was performed at the age of 1 hour by Demmer [66] (the youngest ever recorded), celiotomy was undertaken to relieve an irreducible umbilical hernia, the atresia not being discovered until the abdomen was opened.

Instances occurred of low, as well as of high, atresias operated on relatively late in the course of the disease, with successful results in both types. Many reports give ample testimony that strangulation or perforation or both, can occur in the proximal segment within the first forty-eight hours of life.[67] Because of these dangers (and the difficulty of judging their imminence), it would seem wise to operate on infants with this obstruction as soon as the diagnosis is made, but only after the necessary time has been allowed for determining and correcting the infant's fluid and electrolyte imbalance and for reducing any intestinal distention which may be present.

To date, available statistics do not justify any conclusions as to the mortality rates of high versus low atresias. Of the 52 patients operated on by Ladd and Gross,[21] 5 had duodenal lesions, with an operative mortality of 80 per cent; 6, jejunal atresias, with an operative mortality of 50 per cent, and 34, ileal atresias, with an operative mortality of 91 per cent. Judging from the series of cases of successfully treated, complete atresias of the small bowel listed in table 2

66. Demmer, F.: Atresia ilei: Resectio ileocoecalis; Heilung, Arch. f. klin. Chir. **147**:471, 1927.

67. Sweet and Robertson.[60] Ladd, W. E.: Béla Shick Lecture: The Choice of Time and Type of Operation in Surgery of Early Life, J. Mt. Sinai Hosp. **10**:389, 1943. Moses, E.: Atresia of the Terminal Portion of the Ileum, with Perforation in a Premature Infant, Am. J. Dis. Child. **62**:141 (July) 1941.

TABLE 3.—*Cases of Congenital Atresias of the Small Intestine in Which the Completeness of the Atresia Was Probable But Not Certain and Treatment Was Successful*

Reported by	Date of Operation	Site of Atresia	Single or Multiple	Age at Operation	Surgical Procedure
Weeks, A., and Delpratt, G. O.: S. Clin. North America **7**: 1193, 1927	1916	Third part of duodenum	Single	6 days	Gastrojejunostomy
Higgins, T. T.: Brit. J. Surg. **11**: 592, 1923-1924	5/ 2/1922	Duodenojejunal junction	Single	23 days	Posterior gastrojejunostomy
Loitman, 1927 [30]	1924 (?)	Duodenum	Single	4 days	Posterior gastrojejunostomy
Bolling, R. W.: Ann Surg. **83**: 543, 1926...	10/22/1925	Duodenum	Single	9 days	Duodenojejunostomy
Cameron, H. C.,* in discussion on MacLennan, A.: Brit. M. J. **2**: 818, 1927	Not given	Duodenum	Single	Not given	Posterior gastrojejunostomy
Walker, T. D.; Falkener, W. W., and Horsley, J. S.: Virginia M. Monthly **62**: 141, 1935	5/ 6/1934	Duodenum	Single	5 days	Gastroenterostomy
Donovan, E. J.: Ann. Surg. **103**: 455, 1936	Nov. 1934 (?) 1/27/1935	Duodenojejunal junction Duodenojejunal junction	Single Single	9 or 10 days 17 or 18 days	Anterior duodenojejunostomy Anterior duodenojejunostomy
Tallerman, K. H., and Levi, O.: Proc. Roy. Soc. Med. **31**: 761, 1938	11/21/1937 12/10/1939	Duodenum Duodenojejunal junction	Single Single	(1) 6 days (2) 9 days 8 days	(1) Anterior gastroenterostomy (2) Gastrostomy Transcolic duodenojejunostomy
Miller, 1939 [44]	11/16/1938	Third part of duodenum	Single	38 days	Duodenojejunostomy
Truesdale, P. E., in discussion on Miller [44]	7/10/1938	Duodenojejunal junction	Single	4 days	Duodenojejunostomy
Duckett, J. W.: Ann. Surg. **116**: 321, 1942	12/11/1941	Duodenojejunal junction	Single	2 days	Duodenojejunostomy

* A case, possibly the same one, was discussed by Cameron in the British Medical Journal **1**: 765 (April 25) 1925. He mentioned that a posterior gastroenterostomy was performed, and from the description the obstructive lesion was stenosis, not atresia, of the duodenum.

(which includes the 7 cases of recovery among the 52 cases of Ladd and Gross), one gets the impression that patients with jejunal or ileal atresias have a prognosis as good as, if not better than, patients with duodenal atresias. Of the present group of 36 cases, recovery followed treatment of duodenal atresia in 14, operation for jejunal atresia in 7 and surgical treatment of ileal atresia in 15. It is obvious that the value of these figures is greatly reduced by lack of information on the number of each type of operation that were unsuccessful.

In some cases the atresias may be so numerous and complex that they defeat even consideration of repair. In the group of 36 cases of atresias successfully operated on (table 2) there were 4 instances of multiple atresias, in 1 of which (Duncan and associates [68]) two areas of stenosis were present in addition to multiple atresias. In Arnheim's [27] unusual case, two atresias of the ileum were present, and staged operations were performed. At the first operation, an ileostomy was performed, the section of the ileum containing the atresic portion was removed and the proximal and distal ends of the ileum were exteriorized; at a second procedure, two days later, ileocolostomy was performed; at a third operation, about two months later, it was discovered that the ileocolostomy, which had by-passed the original ileostomy, had also fortuitously detoured around a second, and previously undiscovered, ileal atresia.

The presence of multiple atresias presupposes the presence of blind loops of bowel, which demand some decision as to their disposal. These isolated loops may vary in length, and some have been observed to be perforated at the time of operation. Perforation, or threatened or actual strangulation, obviously makes resection mandatory.

In some cases (Corkill and Corkill [69] Duncan and associates,[68] Erb and Smith [29]) otherwise uncomplicated blind loops were left in situ, and the inquiry naturally arises as to their fate. Their later existence is apparently a dormant one, for among successfully treated patients no report has as yet been found of such a blind loop subsequently perforating, strangulating or assuming the proportions of a cyst.

In the first case here reported, a small blind loop of ileum (fig. 2) lay alongside and parallel to the distal stump. This loop had some features of duplication of the ileum, and it was resected along with a part of the distal stump.

In the choice of an operative procedure, a final plan should not be formulated until the full extent of the abnormalities of the bowel is

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68. Duncan, P. A.; Wearn, F. S.; Jackson, H. F., and Waldron, W. S.: Successful Surgical Treatment of Multiple Atresias (Aplasias) of the Small Intestine in a Premature Infant, J. A. M. A. **123**:764 (Nov. 20) 1943.

69. Corkill, T. F., and Corkill, H. K.: Congenital Atresia of the Ileum, Australian & New Zealand J. Surg. **3**:352, 1934.

known. In cases of duodenal atresia, gastrojejunostomy and duodenojejunostomy have both succeeded, but instances are recorded (Sweet and Robertson [60]) in which gastrojejunostomy failed and was followed by a successful duodenojejunostomy. Both anterior and posterior procedures have succeeded; so it would seem to be sound judgment to select the more feasible procedure. In the patient of Jones and Morton,[70] a duodenotomy was performed and a complete septum removed by fulguration.

In cases of low obstruction, the atresia or atresias must be circumvented, preferably with a primary side to side anastomosis. There have been 4 successful instances in which a proximal catheter enterostomy was performed in addition to a side to side anastomosis (Carter [71]; Corkill and Corkill [69]; Miller and associates [72]).

Enterostomy alone used as a surgical measure to treat atresia of the small bowel has been followed by an appalling mortality, and, to date, only 3 infants so treated have survived. In small infants it is difficult to compensate for the loss of intestinal content through the enterostomy by parenteral administration of fluid for any considerable period. In Arnheim's patient [27] a side to side ileocolostomy was performed thirty-four hours after a primary ileostomy. The case described by Martin and Elkin [73] is unique, for thirty days elapsed between the ileostomy and the final anastomosis. The interval between stages in the case of Ladd and Gross [21] is not recorded, but they expressed the belief that not more than two or three days should elapse between establishing an enterostomy and completing the anastomosis.[74]

REPORT OF CASES

CASE 1.—N. P. M., a white girl, was delivered spontaneously in the North Carolina Baptist Hospital on Aug. 3, 1945, six weeks prematurely, after an uncomplicated pregnancy and labor. The mother, aged 35; the father, aged 40, and 3 siblings, aged 19, 17 and 14 years, respectively, were all living and well. The infant weighed 5 pounds 9 ounces (2,523 Gm.) at birth, and physical examination showed nothing remarkable. Three hours after delivery she vomited a

70. Jones, T. B., and Morton, J. J.: Congenital Malformations of the Intestine in Children, Am. J. Surg. **39**:382, 1938.

71. Carter, R. F.: Congenital Occlusion of the Duodenum and Small Intestine: A Clinical Consideration with Report of Two Successful Cases, J. Pediat. **2**:27, 1933.

72. Miller, E. M.; Greengard, J.; Raycroft, W. B., and McFadden, I.: Congenital Atresia of the Duodenum and of the Ileum: Report of Two Cases with Successful Results Following Operation, Am. J. Dis. Child. **66**:272 (Sept.) 1943.

73. Martin, J. D., Jr., and Elkin, D. C.: Congenital Atresia of the Intestine, Ann. Surg. **105**:192, 1937.

74. In 1940, Lee [20] reported on 2 infants with almost complete duodenal occlusion, 1 of whom was successfully fed for eight months via a jejunostomy tube. A posterior gastroenterostomy was then performed, and the child recovered.

moderate amount of greenish, mucoid material and became cyanotic. Cyanosis was relieved by aspiration of secretions from the mouth and pharynx, but she continued to have bouts of vomiting and cyanosis. Twelve hours after birth she was fed a small amount of 5 per cent dextrose solution, and two hours after that she again had projectile vomiting and became cyanotic.[75] Examination then revealed moderate abdominal distention, and outlines of loops of the small bowel could be traced on the abdominal wall. Plain roentgenograms of the abdomen showed extreme gaseous distention of several loops of the small bowel, with irregular pattern and an irregular calcification in the right lower quadrant (fig. 1). Eighteen hours after birth, the infant passed a single stool, consisting of a small, cylindric, greenish, gelatinous plug, which on examination by Farber's technic,[56] revealed no epithelial cells. It also contained no bile.

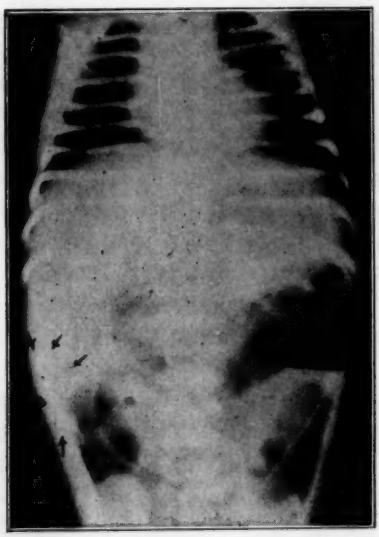

Fig. 1 (case 1).—Preoperative plain roentgenogram. Note calcified areas in right lower quadrant.

Surgical consultation was obtained, and the child was transferred to the pediatric surgical service, with a provisional diagnosis of obstruction of the small bowel, due to meconium ileus, atresia, faulty rotation or adhesive bands. Continuous gastric suction was begun, and the infant received fluids parenterally and a transfusion of whole blood at 30 hours of age, preceding celiotomy.

On August 4, with the patient under ether anesthesia, induced with the open drop method, the abdomen was opened through a right rectus incision, and several loops of extremely distended small bowel protruded, along with loops of greatly contracted small bowel. The distended bowel measured 3 cm., and the collapsed bowel 8 to 10 mm., in diameter. There was pronounced congestion of the dis-

75. In order to reduce the danger from aspiration of vomitus in congenital abnormalities, no milk feedings are offered to infants in our nursery until two feedings of a solution of dextrose and isotonic solution of sodium chloride are retained.

tended loops with bluish black discoloration, dulness of the serosa and a plastic serosal exudate. The mesenteric lymph nodes had a diameter of 6 to 10 mm. There was torsion of the distended portion of the bowel on its longitudinal axis, with adhesions between various loops. The lower portion of the ileum ended blindly in a completely closed pouch. The distal stump, which was 25 cm. proximal to the ileocecal valve, was lying free in the peritoneal cavity and had no connection with the proximal stump. About 8 cm. from the end of the distal stump, there was a tiny blind loop of bowel lying in the mesentery. It was 8 mm. in diameter and 4 cm. long and resembled an intestinal duplication (fig. 2). Because of anxiety concerning blood supply to the stumps, portions of each were resected for a distance of 12 cm.; the ends were closed, and a side to side anastomosis

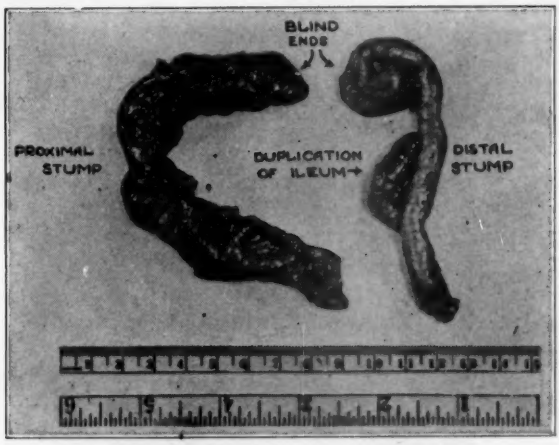

Fig. 2 (case 1).—Blind loop of bowel removed surgically.

was done, using an inner layer of sutures of 000 chromic surgical gut U. S. P. and an outer layer of arterial silk sutures. No other gastrointestinal malformations were observed. Sulfanilamide powder, 2.5 Gm., was placed in the peritoneal cavity and the wound closed without drainage.

After operation, continuous gastric suction was maintained, oral feedings were withheld, and the child was given intravenous infusions of blood, plasma, dextrose, isotonic solution of sodium chloride or one-sixth molar lactate solution, the choice of fluids depending on determinations of blood chemical values. On the third postoperative day, small oral feedings of 5 per cent dextrose in saline solution were begun, and the gastric suction tube was clamped off for increasing periods after each feeding. Caloric intake was increased gradually by feeding successively a mixture of 10 per cent "amigen" and 10 per cent dextrose, skimmed milk and, finally, a dilute evaporated milk formula with supplementary vitamins. During the first week after operation, oral intake totaled 1,630 cc., while fluid aspirated through the gastric tube totaled 1,530 cc. In the same period the infant received a total of 1,825 cc. of fluids parenterally. On a plain roentgenogram of her abdomen taken four days after operation (fig. 3), the calcified shadows seen on the preoperative film (fig. 1) were no longer present.

On the second postoperative day, the infant passed a stool similar in appearance to the first one described, and on the fourth postoperative day she began

having frequent, small, brownish, viscid stools, which subsequently became brownish yellow and pasty and gave a positive reaction for bile.

She received sulfadiazine, 0.5 Gm. per day, for the first twelve postoperative days. On the twentieth postoperative day a stitch abscess developed, which healed after removal of a silk suture and administration of sulfadiazine and penicillin.

Her weight fell to 4 pounds 7 ounces (2,013 Gm.) on the eighth postoperative day. A slow, steady gain in weight then ensued, and she was discharged on the twenty-seventh postoperative day, weighing 5 pounds 7 ounces (2,466 Gm.). The appearance of the patient on the thirteenth postoperative day is shown in figure 4.

At 2 months of age, the formula was changed to 2 per cent lactic acid milk because of slow gain in weight and the passage of three to four large, frothy stools a day. Gain in weight and appearance of the stools improved somewhat on this low fat diet, but she continued to have two to three bulky stools each day.

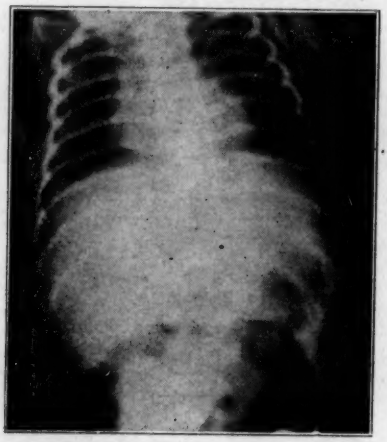

Fig. 3 (case 1).—Plain roentgenogram taken on fourth postoperative day.

Solid foods were added to the diet when she was 3 months of age, and they were taken well. In spite of an exceptionally good appetite and a more than adequate caloric intake, the infant appeared poorly nourished for several months, with large, prominent abdomen and wasted buttocks and extremities. At about 6 months of age, her appearance improved decidedly, and since that time her nutritional status has improved steadily.

At 8½ months of age she was readmitted to the hospital for study. Because of the calcified shadows in the preoperative roentgenogram, the inspissated meconium in the proximal bowel stump, and the slow gain in weight and the bulky stools, it was felt that the possibility of fibrocystic pancreatic disease should be investigated.

Assay of pancreatic juice by the Andersen and Early [76] modification of the Fermi method showed tryptic digestion comparable to 24 viscosimetric units, a low normal value but sufficient, according to Andersen and Early, to rule out

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76. Andersen, D. H., and Early, M. V.: Method of Assaying Trypsin Suitable for Routine Use in Diagnosis of Congenital Pancreatic Deficiency, Am. J. Dis. Child. **63**:891 (May) 1942.

pancreatic fibrosis. The stool fat was 16.4 per cent of the wet weight, two thirds occurring as free fatty acids.

The report of roentgenographic study of the small bowel was as follows: "A barium sulfate meal showed no lesion in the stomach or the esophagus. Progress of the meal through the small bowel was somewhat retarded, and there were abnormally dilated loops of bowel and changes in the mucosal pattern of questionable significance. At five hours the barium had passed well into the descending colon and rectum. At twenty-four hours there was no residual barium in the small intestine, and the colon did not appear abnormal. The operative stoma was not visualized." A roentgenogram of the chest and studies of the blood and urine showed a condition within normal limits. The appearance of the patient at the age of 14 months is shown in figure 5.

Several observations point to impairment of gut function in this child: slow gain in weight with adequate caloric intake; the bulky

Fig. 4 (case 1).—Appearance of infant on thirteenth postoperative day.

character and increased fat content of the stools, and roentgenographic changes of questionable significance in the intestinal pattern.

That she had a low tolerance to dietary fat was shown by the increased fat content of the stool on a normal diet and by the gain in weight and improvement in the character of the stools on a low fat diet.

One can only speculate as to the nature of this impairment. During the first six months of life, her appearance and behavior strongly suggested congenital fibrocystic pancreatic disease. The demonstration of a low normal value for tryptic activity in the duodenal fluid, together

with her subsequent remarkable improvement in nutrition without specific therapy, led to the abandonment of this possibility.

Motor disturbances resulting from resection and alteration of the continuity of the intestine may cause interference with digestion and absorption of food. This condition is difficult to diagnose roentgenographically in children. Zwerling and Nelson [77] showed that studies of the small bowel of normal infants and children reveal wide variation in the intestinal pattern. It is obvious that resection of a portion of intestine in a premature infant results in a proportionately greater loss

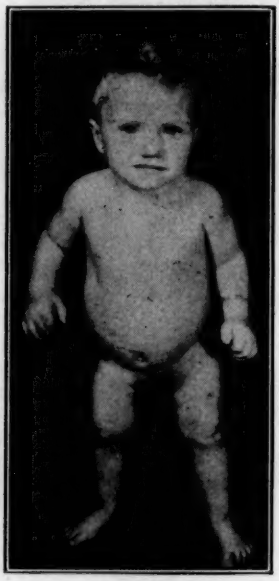

Fig. 5 (case 1).—Appearance of infant at the age of 14 months.

of absorptive surfaces than in an adult. Any or all of these factors may have been operative in this infant. The problem which infants with intestinal atresia present may extend well beyond the period of convalescence following surgical repair.

Case 2.—W. D. C., a white boy, was admitted to the North Carolina Baptist Hospital on Nov. 9, 1946, at the age of 8 days. The child, born by breech presentation, was delivered of a primiparous mother one month prematurely, on Nov. 2, 1946. His weight at birth was 6 pounds 4 ounces (2,835 Gm.), and physical examination showed nothing remarkable. For three days the child was said to nurse well, and he passed a small amount of meconium-like material. On the fourth day of life the child began to regurgitate feedings and became jaundiced. He was taken off breast feedings and given dextrose solution orally. The nonprojectile

77. Zwerling, H., and Nelson, W. E.: The Roentgenological Pattern of the Small Intestine in Infants and Children, Radiology **40**:277, 1943.

regurgitation of bile-stained material continued; the jaundice deepened and a monilial infection of the mouth developed. Fluids had been given parenterally for four days prior to his admission to the hospital.

When admitted to the hospital, the infant had some mongoloid features and was unusually quiet; the upper part of the abdomen was slightly distended. He weighed 5 pounds 4 ounces (2,381 Gm.), was dehydrated and jaundiced and had severe oral moniliasis. The hemoglobin concentration was over 18 Gm. per hundred cubic centimeters of blood. The red cells averaged 6,720,000, and the white cells, 7,300,

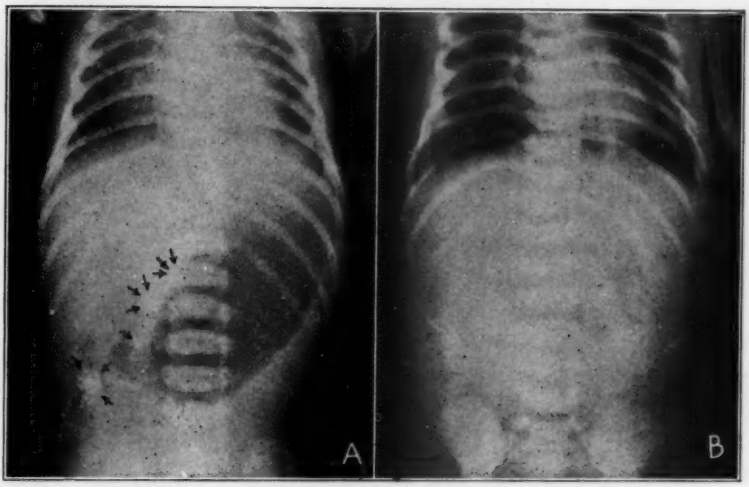

Fig. 6 (case 2).—*A*, preoperative plain roentgenogram. Note calcified areas outlined by arrows; *B*, plain roentgenogram taken on fourth postoperative day. The shadow in the right lower quadrant is made by dressings on the abdomen.

per cubic millimeter. The urine had a p_H of 6, with a 1 plus reaction for albumin, a trace of sugar, no acetone or diacetic acid and a 1 plus reaction for bilirubin. The prothrombin time was 44 seconds (control, 26 seconds). Candida albicans, Neisseria catarrhalis, Staphylococcus albus and alpha streptococci were cultured from the mouth. Meconium removed from the rectum on digital examination was observed to be devoid of squamous epithelial cells when examined bv Farber's technic.

A plain roentgenogram of the abdomen showed the stomach well filled with gas, but no gas was evident distal to it. Several radiopaque areas were seen just to the right of the lumbar portion of the spine (fig. 6*A*). (This child had not had any radiopaque material, and the shadows were not seen on postoperative roentgenograms.)

The diagnostic impression was that of congenital atresia of the upper portion of the small intestine, probably distal to the ampulla of Vater.

The hypoprothrombinemia, thrush and dehydration were energetically treated; multiple vitamins were administered, and on November 10, at the age of 9 days, celiotomy was performed, using ether-oxygen anesthesia.

The stomach and the proximal portion of the duodenum were greatly distended, so that the first portion of the duodenum appeared to be part of the stomach itself, until the thinned-out pyloric muscle was identified. Just distal to the entrance

of the common bile duct into the duodenum, a zone of complete atresia, 1.5 cm. long, was observed, with fibrous adhesive bands attaching this zone to the colon and to the anterior abdominal wall. The remainder of the small and the large bowel was normal. An antecolic, side to side duodenojejunostomy was performed and the abdomen was closed.

After the operation, continuous gastric drainage was maintained for four days, and the child was given parenterally fluids consisting of plasma, whole blood, isotonic solution of sodium chloride and dextrose solution. All vitamins, including a vitamin K preparation, were supplied, and the oral moniliasis was treated with topical applications of gentian violet solutions. Oral feedings of 5 per cent dextrose solution in half-normal solution of sodium chloride were begun on the fifth

Fig. 7 (case 2).—Appearance of patient at the age of 3 months.

day, and on the succeeding days this was replaced by the oral administration of formula. In a plain roentgenogram of the patient's abdomen taken on the fourth postoperative day (fig. 6 *B*), the calcified areas seen in the preoperative roentgenogram were no longer visible.

The child sucked poorly, owing possibly to the thrush infection, and this necessitated dropper feedings for several days. The oral fluid intake was supplemented with parenteral administration of plasma and electrolyte solutions as needed. On this regimen, and in spite of occasional regurgitation, the infant gained weight slowly but steadily, and his weight, which was 5 pounds 2¾ ounces (2,346 Gm.) on the first postoperative day, increased to 5 pounds 13 ounces (2,637 Gm.) at the time of discharge, on the twenty-fourth postoperative day.

A wound infection caused by beta (hemolytic) streptococci and Staph. albus developed on the seventh postoperative day. This infection healed rapidly with the daily administration of penicillin. Hemoglobin values remained at or above 18 Gm. per hundred cubic centimeters during the entire postoperative course, although the red cell count had decreased to 5,140,000 per cubic millimeter by the tenth postoperative day. Stained blood smears showed normochromic and normocytic red

cells, with only an occasional nucleated erythrocyte. Administration of menadione U. S. P., 1 mg., in daily doses was continued until the ninth day after operation, and the plasma prothrombin activity remained well within a safe range.

On the twentieth postoperative day, roentgenographic study of the upper gastrointestinal tract with barium sulfate showed that the stomach was normal and emptied promptly. The anastomosis was not visualized, and progress of the meal through the small bowel was normal.

The child was seen on March 6, 1947, at which time the body measurements were: height, 24 inches (61 cm.); circumference of the head, 15 inches (38 cm.); circumference of the chest, 14 inches (36 cm.), and weight, 11 pounds (4,990 Gm.). The diagnosis of mongolism was definite at this time. An incisional hernia was present (fig. 7), but there were no symptoms or signs referable to the gastrointestinal tract.

COMMENT

The importance of congenital intestinal atresias is much greater than their incidence would tend to indicate because they are amenable to surgical treatment. In most of the children so afflicted, the atretic lesion is the only abnormality present, so that its correction should restore the patient to complete normalcy. This good prognosis emphasizes the importance of early diagnosis and of the prompt institution of supportive and surgical treatment. Probably the greatest single factor in early diagnosis is the close cooperation of the departments of pediatrics and obstetrics in the care of newborn infants in the nursery, so that adequate nursery routines will be devised, aiding early recognition of disorders of the newborn. Undoubtedly, the high mortality still current even among infants in the hands of excellent pediatricians and pediatric surgeons is due to the fact that many of these infants do not reach them until relatively late in the course of the disease.

The nature and location of the opaque areas seen on the preoperative plain roentgenograms of both these patients are of great interest, in view of Neuhauser's [59] opinion that such areas are typical of the presence of fetal meconium peritonitis. In the 2 infants here discussed, a diagnosis of meconium peritonitis could not be made with certainty, for even though the second patient had peritoneal adhesions present, no yellowish plaques of old meconium were present on the peritoneal surfaces. Furthermore, these calcified areas were not present on plain roentgenograms made four days after either operation. It seems probable that in these 2 patients the calcified material was within the intestinal lumen, although this is not entirely certain.

Dr. O. E. Wright delivered and referred the first patient; Dr. Lester Crowell delivered and referred the second patient; Dr. William A. Wolff carried out the chemical studies; Dr. J. P. Rousseau made the roentgenologic examinations; Miss Ruth Martin, record librarian, compiled the statistics on incidence of congenital atresias at the North Carolina Baptist Hospital, and the pediatric house officers and nurses gave invaluable aid in the postoperative care of the patients.

Bowman Gray School of Medicine.

News and Comment

NOTICES

Financial Statement of Fifth International Pediatric Congress.—The condensed financial statement of the Fifth International Congress of Pediatrics, held in New York City on July 14, 15, 16 and 17, 1947, is as follows:

Receipts

Subsidies from pediatric organizations in the United States	
American Academy of Pediatrics (United States members only)	$18,855.00
American Medical Association (Pediatric Section)	3,000.00
American Pediatric Society	1,000.00
Society for Pediatric Research	75.00
Contributions from philanthropic foundations and individuals	40,075.00
Contributions from industrial organizations	60,100.00
Revenue from registration fees	55,005.00
Total receipts	$178,110.00

Expenses

Subsidies to 107 foreign delegates	$97,061.21
Promotional expenses	2,244.64
Secretarial and office salaries	4,602.36
Printing, stationery, postage, telephone, cables	9,444.52
Badges	2,430.50
Rental of space	8,000.00
Translations and translation equipment	5,197.98
Exhibit (expenses other than rental)	10,452.92
Reception, teas, luncheon to official delegates	8,000.00
Banquet	16,000.00
Steamer excursion	5,118.34
Post-Congress tours	1,336.02
Miscellaneous expenses	7,721.01
Total expenses	$178,110.00

Fund Established for Promotion of Therapeutic Investigation.—The American Medical Association has entrusted the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry with a fund to be expended in the promotion of investigations that may have therapeutic interest. The Committee invites applications for grants in this general field, which is conceived very broadly.

In the application there must be an adequate description of the research proposed. Since the grants from the Council may well be small in relation to the total cost of investigations aided, the Committee would appreciate information as to whether the proposed research is a continuation of investigation which has been supported previously by some research fund, and as to whether the work is to be supported in part by a grant, or grants, from other sources. If support is to be received from another grant, the Committee would like to know the name of the organization making the other grant and its amount.

Applications should be in the hands of the Secretary of the Council, 535 North Dearborn Street, Chicago 10, by March 1, 1948. To expedite transmission to members of the Committee, it is asked that six copies (five carbon copies) of each application be sent. Action will not be taken until after all applications are received.

STUART MUDD, M.D., Chairman,
Committee on Therapeutic Research, Council
on Pharmacy and Chemistry.

Hungarian Centenary Congress of Pediatrics.—The Hungarian Medical Trade Union desires to celebrate the centenary of the War of Liberation by arranging a medical convention in Budapest from Sept. 4 to 12, 1948. The Pediatric Section of the Union has arranged for an International Congress of Pediatrics to be held during this week.

Two of the five days of the Congress will be devoted to plenary sessions of all sections. On the other three days the following topics will be discussed: rheumatic fever, toxicosis and the social significance and influence of pediatrics.

Lectures on many other subjects will be also included.

All pediatricians interested in the Congress are invited to participate. Those who expect to attend should communicate with the Centenary Congress Committee, Bokay Janos u. 53, Budapest 8, Hungary. Those who wish to take part in the discussion on one of the main topics or to present a paper on another subject are requested to give the title and a short summary of the report.

GENERAL NEWS

Benjamin Knox Rachford Lectureships.—Dr. Sidney Farber, of Boston, will deliver the sixteenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday evening, Feb. 3, and on Wednesday evening, Feb. 4, 1948, at 8:30, in the auditorium of the Children's Hospital Clinic and Research Building, in Cincinnati. The general title of his lectures will be "The Place of Pathology in the Practice of Pediatrics."

Abstracts from Current Literature

Vitamins; Avitaminoses

A Comparison of the Vitamin C in Mothers and Their Newborn Infants. Lawrence B. Slobody, Reuel A. Benson and Joan Mestern, J. Pediat. **29**: 41 (July) 1946.

The comparative saturations of vitamin C in the tissue of mothers and their newborn infants were determined by means of the intracutaneous injection of a solution of sodium 2, 6-dichlorphenol indophenol. The infants were tested repeatedly during the first eight days of life. It was observed that the infants tended to show a saturation of vitamin C in the tissue irrespective of variations in the vitamin C concentration in the mother.

Grulee Jr., Minneapolis.

Prematurity and Congenital Deformities

Behavior Aspects of the Care of the Premature Infant. Arnold Gesell, J. Pediat. **29**:210 (Aug.) 1946.

The author describes the importance of tonal reactivity as the first evidence of behavior and as an index of the structural maturity of the organism. The possibility that optimal tonus may be provided by suitable close-fitting clothing, judiciously administered daily baths and brief skilful handling, as well as through bedding which imparts a sense of movement with the stirrings of the infant, should definitely have a place in the ideal management of the premature infant. No data referable to specific study are furnished.

Grulee Jr., Minneapolis.

Newborn

The Influence of Human Serum Albumin on Edema in Erythroblastosis Fetalis. Mendel Jacobi, Abraham Litvak and Seymour Gruber, J. Pediat. **29**:177 (Aug.) 1946.

Two infants with erythroblastosis fetalis complicated by severe generalized edema were given concentrated human serum albumin in addition to transfusions. In both patients elimination of edema was effected. The authors suggest that hepatic damage and disturbed blood protein levels are factors causing the production of the edema.

Grulee Jr., Minneapolis.

Treatment of Epidemic Diarrhea of the Newborn. Martin J. Glynn, J. Pediat. **29**:205 (Aug.) 1946.

Epidemic diarrhea of the newborn is discussed concisely, with a succinct, thorough, detailed review of therapy. The judicious use of starvation and subsequent gradual resumption of low caloric feedings, in combination with suitable replacement and subsequent maintenance therapy parenterally administered, are carefully related. The author reports mortality rates of 13 per cent among 91 full term infants under 4 weeks of age and of 17 per cent among 92 premature infants treated in this manner.

Grulee Jr., Minneapolis.

STATISTICAL PROBLEMS OF STILLBIRTH. FRANCISCO J. MENCHACA, Arch. argent. de pediat. **25**:147 (March) 1946.

Before the fight against stillbirths is organized on a rational, scientific basis, reliable statistics are needed. Fundamental methodologic reasons require that the nomenclature of the current "International List of Causes of Death" be followed, as well as the definitions of "stillbirths" and "perinatal mortality" given by the International Institute of Statistics. The accepted terminology must be widely disseminated, not only among physicians and obstetricians, but also among all those who deal with the statistics of stillbirth. The criteria for diagnosis that obstetrics will maintain in the next revision of the "Nomenclature of the Causes of Death" must be prepared sufficiently in advance.

It is necessary to secure accurate birth records and to perform autopsies on stillborn infants in order to establish the true causes of death. Social service is indispensable in establishing the cause of many stillbirths, and in reducing the mortality efficiently.

ROJAS, BOSTON.

Acute Contagious Diseases

TWO CASES OF WATERHOUSE-FRIDERICHSEN SYNDROME IN THE SAME FAMILY, ONE WITH RECOVERY UNDER PENICILLIN THERAPY. J. J. HOFFMAN and A. E. MAMELOK, Arch. Pediat. **63**:391, (Aug.) 1946.

Two cases of epidemic cerebrospinal meningitis (Waterhouse-Friderichsen syndrome) are presented. The patients were brothers, 13 and 15 years of age. The younger patient became ill first, with all the classic symptoms, and recovered after intensive therapy with plasma, dextrose and saline solutions, adrenal cortex extract, "percorten" (a proprietary preparation of desoxycorticosterone acetate), sulfadiazine and penicillin. Type II meningococci was cultured from the blood. Massive sloughing of the purpuric areas occurred, and residual pain in the joints lasted several weeks, but the prognosis was good.

The second patient was found dead in bed two days after his younger brother became ill. Autopsy revealed massive areas of purpura in the skin and massive hemorrhages in the adrenal glands. No culture of the blood was obtained.

The authors present a detailed review of the literature and a discussion of the optimal method of treatment. This treatment should include replacement therapy to compensate for involvement of the adrenal medulla and adrenal cortex, chemotherapy and general supportive measures. Emphasis is placed on rapid diagnosis and treatment.

DAVIS, DENVER.

IMMUNIZATION AGAINST WHOOPING COUGH. J. H. LAPIN, J. Pediat. **29**:90 (July) 1946.

The author reviews recently published experiences in a brief and concise discussion of immunization against whooping cough. He adds his observations of a series of 20 infants inoculated between 3 and 6 months of age, who were subjected to rapid agglutination tests for antibody titer three months after inoculation. Negative reactions were obtained in 60 per cent of this series of patients. The use of alum-precipitated preparations and of combinations of pertussis vaccine with diphtheria and/or tetanus toxoids is condemned as causing unnecessarily severe reactions, even formation of abscesses, in an appreciable number of infants. Pertussis vaccine alone in a concentration of 40,000,000,000 per cubic centimeter is recommended. Inoculation, in the opinion of the author, should begin when the infant is 6 to 9 months of age, with one injection per week until a total of 80,000,000,000 to 120,000,000,000 units have been given in three injections.

GRULEE JR., MINNEAPOLIS.

MUMPS: TECHNIQUES OF LABORATORY DIAGNOSIS, TESTS FOR SUSCEPTIBILITY, AND EXPERIMENTS ON SPECIFIC PROPHYLAXIS. JOHN F. ENDERS, J. Pediat. **29**:129 (Aug.) 1946.

A comprehensive discussion of the application of the complement fixation tests in the diagnosis of mumps and of the differential diagnosis of conditions simulating mumps meningoencephalitis is presented. Data are offered in support of the use of intradermal cutaneous testing with heat-inactivated virus as a measure of immunization against mumps. Clinical observation has indicated the ineffectiveness in prophylaxis of gamma globulin prepared from large pools of normal plasma. The results from the use of formalized vaccine for protection against the disease are encouraging, if the vaccine is given prior to the incubation period of the disease. Finally, studies currently in progress on the production of active immunity through the use of mumps virus attenuated by egg passage are discussed.

GRULEE JR., Minneapolis.

MENINGOCOCCAEMIA: PART III. BACTERIOLOGY, SEROLOGY AND ETIOLOGY. W. R. LOGAN, Edinburgh M. J. **53**:235 (May) 1946.

The author discusses the mode of infection in meningococcic meningitis and its epidemiology. The primary infection is in the nasopharynx and is acquired from carriers, rather than from persons with active meningitis. Not all observers are agreed that there is an obvious local inflammation within the nasopharyngeal tract. The present view is that meningococcic meningitis may follow invasion of the blood stream by way of the lymphatics from the nasopharynx. The primary site involved in the central nervous system is the lateral ventricles, through the choroid plexuses. It is probably a correct assumption that the portal of entry in meningococcemia is the same as that in meningitis, but it has not been so proved bacteriologically. The author discusses neurologic types of meningococci, as well as the types in meningococcemia; he makes a comparison of the pathogenicity and virulence of group I and group II as regards mortality and duration of the illness. The author discusses the intermittency in meningococcemia and the immunologic reactions in both meningococcemia and meningitis. He concludes that there is no evidence of the production of more protective substances in meningococcemia than in meningitis. Phagocytosis and lysis represent the first stage of a defensive process and are regarded as a protective action.

In most cases the disease was diagnosed by means of blood culture. The growth on culture usually is slow, requiring three or four days on the average. There is no positive information as to the optimal time for obtaining blood for culture in cases of meningococcemia; occasionally a positive culture may be obtained in a period of asphyxia. The author discusses the bacteriologic examination of cutaneous lesions. In acute and fulminating stages of infection, there are many meningococci in and beneath the skin. Toxins are released from the disintegrated micro-organisms which probably affect the endothelium of the capillaries, both in acute and chronic meningococcemia.

NEFF, Kansas City, Mo.

Acute Infectious Diseases

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. V. STAPHYLOCOCCAL EMPYEMA: THE IMPORTANCE OF PYOPNEUMOTHORAX AS A COMPLICATION. GILBERT B. FORBES, J. Pediat. **29**:45 (July) 1946.

A careful and complete discussion of the cases of staphylococcic empyema observed at the St. Louis Children's Hospital during the past ten years is presented, not including those in which penicillin was used. One half of all cases of empyema

in infants under 1 year of age were caused by the staphylococci, as compared with 10 per cent in the entire pediatric age group. The pathologic changes caused by staphylococcic pneumonia are discussed in relation to the frequent occurrence of bronchopleural fistulas and consequent pyopneumothorax. The latter complication is considered by the author as being most dangerous and demanding immediate closed intercostal syphon drainage. Pyopneumothorax occurred in 2 of every 5 cases in the series. The total mortality rate of 26.2 per cent is discussed in relation to the progressively improved management of the patients. Early diagnosis and vigorous therapy, including chemotherapy with sulfonamide compounds, are emphasized, as well as the application of all suitable supportive measures and the prompt surgical drainage of the pyopneumothorax. It is concluded that antistaphylococcic serum is of limited usefulness and that sulfonamide drugs, though not highly effective, should be used.

GRULEE JR., Minneapolis

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY. VI: ACUTE ILIAC LYMPHADENITIS. MERL J. CARSON and ALEXIS F. HARTMANN, J. Pediat. **29**:183 (Aug.) 1946.

The clinical syndrome presented by 11 patients with iliac lymphadenitis is discussed, together with the differential diagnosis and treatment of the condition. In the authors' opinion, pain in the abdomen, hip, thigh or knee, psoas spasm with protective flexion of the thigh on the abdomen and free motion of the hip joint, except for extension of the thigh, are particularly suggestive signs. Fever and leukocytosis are the commonest observations and hemolytic Staphylococcus aureus the most frequent causative organism. Subcutaneous administration of penicillin, in addition to sulfonamide therapy, is recommended in treatment.

GRULEE JR., Minneapolis.

LEISHMANIASIS IN SARDINIA. G. MARIA DORE, Pediatria **55**:109 (Jan.-March) 1947.

The author describes 5 cases of visceral leishmaniasis observed since 1940 among children living in Sassari province.

FROM THE AUTHOR'S ABSTRACT.

TESTS OF INFECTIVITY WITH OXYURIS. N. H. SWELLENGREBEL, Nederl. tijdschr. v. geneesk. **90**:762 (July 6) 1946.

As it was unknown whether desiccated eggs of Oxyuris, especially those present in dust, could still develop into full grown worms, the author made this investigation. The dust was taken from an open air school were almost 100 per cent of the children was infected with Oxyuris. The dust, at least three days old, was washed in 0.2 per cent hydrochloric acid and centrifuged; then the number of eggs was counted. The dust was then dropped on bread and eaten. The number of eggs swallowed by each volunteer varied between 40 and 80.

Six of the eight tests with the egg-laden dust produced the infection. To determine exactly the first manifestation, a perianal preparation was made each day; the shortest incubation period appeared to be thirty-seven days. The excretion of the worms, as shown by the presence of eggs, lasted twelve to twenty-seven days. It appeared that such an infection with Oxyuris disappeared spontaneously if contamination with fingers or dust could be prevented. Eggs from dust always produce slight infection, whereas eggs from fingers may give rise to severe infections.

As regards the treatment of oxyuriasis, one must always bear in mind that infection from dust is a factor which is not under control. For this reason, the author rejects severe purging of patients with oxyuriasis, as well as the administration of high enemas. He is of opinion that only so-called active oxyuriasis, i. e., infection giving rise to complaints, should be treated.

The treatment should not be complicated, and only nonirritating methods should be used until the outlook for radical means of combating the infection has become better. New insight into the significance of egg-laden dust in schools makes the author skeptical as to the possibility of stamping out an Oxyuris infection in a whole family.

VAN CREVELD, Amsterdam, The Netherlands.

TEN YEARS OF SPRAYING HOUSES AGAINST MALARIA. N. H. SWELLENGREBEL and H. KRAAN, Nederl. tijdschr. v. geneesk. **90**:1377 (Oct. 12) 1946.

The authors report on ten years' observation on the effect of house spraying with pyrethrum solutions during the period of transmission of malaria (August to October). Malaria was greatly reduced in rural areas, and these areas withstood even the severe epidemic which started in 1944. In urban areas the results were unsatisfactory.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

ELECTROPHORETIC ISOLATION OF A CIRCULATING ANTICOAGULANT. F. L. MUNRO and MURIEL PLATT MUNRO, J. Clin. Investigation **25**:814 (Nov.) 1946.

Plasma from a patient with hemophilia was electrophoretically fractionated in a Tiselius cell. Two fractions were removed from each side of the cell under observation with the Toepler Schieren method. The fractions were tested for anticoagulant activity by determination of the extent to which they would prolong the coagulation time of recalcified normal plasma.

Only the fractions containing gamma globulin displayed anticoagulant activity. Both the gamma globulin plus fibrinogen fraction and the gamma and beta globulin plus fibrinogen fraction showed anticoagulant activity. On removal of fibrinogen, and with further electrophoretic fractionation, it was shown that the anticoagulant activity was within the gamma globulin fraction.

BRODSKY, Cincinnati.

LABORATORY AND CLINICAL CRITERIA OF RHEUMATIC CARDITIS IN CHILDREN. L. M. TARAN, J. Pediat. **29**:77 (July) 1946.

The author presents a series of 200 patients from 6 to 14 years of age who had rheumatic fever without signs of cardiac failure. They were studied under well controlled conditions for at least six months after the onset of carditis. In a search for suitable laboratory criteria for determining the presence of carditis, the following measurements were made and were found inadequate: leukocyte counts, temperature, auriculoventricular conduction time, pulse rate, sedimentation rate, gain in weight, hemoglobin values and vital capacity. The results of the last mentioned test were considered the most helpful. Similarly, the following clinical criteria were appraised: fatigability, emotionality, degree of pallor, lability of pulse rate, changes in cardiac rhythm, evidence of progressive cardiac damage and the evanescent quality of heart sounds and murmurs. In many instances these factors were helpful, but in no case could they be considered pathognomonic. The author concludes that clinical judgment based on long and careful observation of patients with rheumatic fever is the best criterion. The importance of rest in bed as treatment is emphasized.

GRULEE JR., Minneapolis.

HISTORICAL, CLINICAL, HEMATOLOGIC AND BIOCHEMICAL REPORTS AND PATHOGENIC CONSIDERATION OF TWENTY-FIVE CASES OF MEGALOBLASTIC HYPERCHROMIC ANEMIA IN EARLY INFANCY. MAURO AMATO, Pediatria **54**:71, 1946.

During the last four years the author had the opportunity to observe in the pediatric clinic of Naples 25 cases of megaloblastic hyperchromic anemia in infants. Because of the rarity of this syndrome during the first months of life, and because there are few references to it in the literature, the author calls attention to the principal anamnestic, clinical, hematologic and biochemical data obtained in these cases.

The anemia in these cases responded rapidly to the administration of liver extract with a high content of the anti-pernicious-anemia principle, whereas the oral administration of large doses of beer ferment, in some instances for fifteen to thirty days before the initiation of liver therapy, gave no results.

In none of the children was recurrence observed; so it seems that this form of anemia is susceptible to definite, or at least prolonged, remission.

The author discusses the etiologic and pathogenic aspects and concludes that, in the cases he observed, one can speak of Biermer's (pernicious) anemia only when it is shown that the form of anemia is cryptogenetic and is due to a deficiency of Castle's intrinsic factor.

The disturbance of the production of the intrinsic principles seems usually to be functional; the author, therefore, advances the hypothesis that children with this type of anemia at birth have a functional incapacity to produce this ferment and that administration of a preparation containing the anti-pernicious-anemia principle will stimulate and carry into action the production of this ferment.

FROM THE AUTHOR'S ABSTRACT.

NONLIPID RETICULOENDOTHELIOSIS (ACUTE CRYPTOGENIC ALEUKEMIC RETICULOENDOTHELIOSIS). GUSTAVO PITTALUGA, AGUSTÍN CASTELLANOS, ENRIQUE GALÁN JUAN JIMÉNEZ and LUIS BARRERAS, Rev. cubana de pediat. **18**:125 (March) 1946.

In a case of nonlipid reticuloendotheliosis in a boy 9 years of age the clinical picture was characterized by gradual onset of pallor and by asthenia, anorexia, general malaise and protracted fever. The initial symptoms were referable to the respiratory tract, with clinical and roentgenologic evidence of pulmonary consolidation. There were splenomegaly, moderate hepatomegaly and polyadenopathy. The disease lasted four months. The child died in collapse, as a result of uncontrollable hemorrhage from the lungs.

Hematologically, there were progressive anemia, leukopenia, neutropenia and thrombopenia. There finally appeared in the blood large numbers of atypical cells with the morphologic character of histiocytes. Examination of specimens obtained by puncture from the sternal bone marrow, the lung, the spleen, the liver and the lymph nodes permitted the diagnosis of nonlipid reticuloendotheliosis to be made during the child's life.

The cause of the process was not determined. There was a generalized hyperplasia of the cells of the reticuloendothelial system, both monocytes and histiocytes. No lipid foam cells were observed at any time. The authors expressed the opinion that the patient had a condition differing from that known as Letterer-Siwe disease. There were lesions in the bones, and the blood picture varied from that reported in the aforementioned disease.

There is a detailed discussion of the literature and of the distinct clinical and anatomic entities referred to as "reticuloendotheliosis."

KEITH, Rochester, Minn.

Diseases of Nose, Throat and Ear

CRANIOPHARYNGIOMAS IN CHILDREN. F. D. INGRAHAM and H. W. SCOTT JR., J. Pediat. **29**:95 (July) 1946.

The authors present their experience with 16 cases of craniopharyngioma, of which 12 were from 1 clinic and constituted 6.3 per cent of the intracranial tumors studied in that clinic over thirteen years. Two reports of illustrative cases are included. The histologic differentiation of the tumors as mucoid epithelial cysts, adamantinomas or squamous epitheliomas is described. The authors discuss the cardinal symptoms of visual disturbances, intracranial hypertension, hypophysial disorders and hypothalamic disorders. Aids to diagnosis, such as discovery on roentgenographic examination of the skull of suprasellar calcification and evidence of increased intracranial pressure, are pointed out. Although, frequently, complicated neurosurgical approaches are necessary in individual cases, frontal craniotomy, with resection of a portion of the cyst, is recommended whenever possible. The authors express the opinion that postsurgical irradiation should have further trial.

GRULEE JR., Minneapolis.

Diseases of Lungs, Pleura and Mediastinum

CONGENITAL CYSTIC DISEASE OF THE LUNG. JOE GARDNER, New Orleans M. & S. J. **99**:15 (July) 1946.

Congenital cystic disease of the lung is not a rare condition. Because of the variety of its manifestations it has been described in medical literature under eighteen names, which are enumerated in the article. The author gives two popular classifications—Koontz's and Sellers'.

The disease was first described by Fontanus in 1638. Interest was renewed after the report by Koontz, in 1925. At present reports of the disease are fairly common. In many cases the condition is asymptomatic, being accidentally discovered at autopsy. Bronchiectasis is the commonest condition to be confused with cystic disease. One or both lungs may be involved. Incidence is similar for the two sexes. No routine treatment can be given, owing to the wide variation in types.

BERKLEY, Beverly Hills, Calif.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE CONTROL OF DIARRHEA BY TOMATO POMACE. LESTER M. MORRISON, Am. J. Digest. Dis. **13**:196 (June) 1946.

Pulverized, dehydrated tomato pulp (tomato pomace) was used to treat more than 100 patients with various types of diarrhea. One tablespoon (15 cc.) of pomace was given every three hours to the patient with moderate diarrhea, and 1 tablespoon after every bowel movement to the patient with severe diarrhea. Relief of symptoms and normal stools were observed after twenty-four hours in the usual case and after forty-eight hours in the severe case. Nine cases are reported in detail. No control series is mentioned.

KIMBALL, Evanston, Ill.

FOREIGN BODY IN DUODENUM CAUSING URINARY DISTURBANCE. E. T. MCENERY and P. F. FOX, J. Pediat. **29**:226 (Aug.) 1946.

A case is reported of persistent hematuria, albuminuria and pyuria which were attributable to inflammatory adhesions in the region of the third portion of the

duodenum and involving the right kidney, resulting from the presence of a bobby pin within the duodenal lumen. Uneventful recovery followed surgical removal of the foreign body.

GRULEE JR., Minneapolis.

HIRSCHSPRUNG'S DISEASE. WILFRID SHELDON, Practitioner **156**:425 (June) 1946.

Congenital dilatation of the colon (Hirschsprung's disease) is characterized by progressive distention, elongation and hypertrophy of the large intestine and occurs more frequently in male patients. Symptoms appear within the first few weeks of life; the course is unknown. The abnormality extends from the cecum to the rectum, with the most pronounced distention in the pelvic portion of the colon. Occasionally, the lower end of the small intestine is involved, but the anal canal is not affected. There is no demonstrable obstruction by valves or bands. True Hirschsprung's disease is to be distinguished from dilatation of the colon arising from a demonstrable obstruction, such as a rectal stricture. The two most striking symptoms are conspicuous enlargement of the abdomen and severe constipation. Of 30 patients with Hirschsprung's disease, 14 died in the first year and 2 in the first month. A few children with the disorder reach adult life.

Medical treatment consists chiefly in the administration of drugs which stimulate the action of the parasympathetic nervous system, such as methacholine chloride U. S. P. (acetyl-β-methylcholine chloride), pilocarpine, physostigmine and neostigmine. Atropine derivatives have been used, with reportedly good results.

Surgical treatment recently has consisted of bilateral division of the second to the fourth lumbar sympathetic rami. Good results have followed this operation in that the child has a daily bowel action without the use of laxatives.

Spinal anesthesia, which to be effective should be complete to the fifth thoracic root, has produced permanent benefit, but usually constipation gradually returns. This procedure serves as a guide in the selection of patients most apt to benefit permanently from sympathectomy. No known treatment reduces appreciably the size of the abdomen.

DIARRHEAS OF VIRUS ORIGIN IN SUCKLINGS. JACQUES GERBEAUX, Arch. franç. d. pediat. **3**:420, 1946.

The notable contributions of American clinicians in the clarification of severe diarrheas of infants and children are reviewed. Particular credit is given to the investigations of Barenberg, Baker, Light and Hodes, Katherine Dodd and John Budding. The isolation of a virus hitherto unrecognized in cases of stomatitis and diarrhea is discussed, and the clinical features of the disease, together with the results of inoculation, are adequately presented.

AMESSE, Denver.

HEPATITIS WITH SYMPTOMS OF CIRRHOSIS OF THE LIVER IN A BABY. A. VAN WESTRIENEN, Nederl. tijdschr. v. geneesk. **90**:684 (June 22) 1946.

During an epidemic of hepatitis a baby of 6 months had slight symptoms of hepatitis without jaundice, followed by alarming symptoms of cirrhosis of the liver. Later, all these symptoms disappeared and the baby completely recovered.

VAN CREVELD, Amsterdam, The Netherlands.

FAMILIAL CIRRHOSIS OF THE LIVER AND OSTEOPOROSIS. A. G. SCHOO, Nederl. tijdschr. v. geneesk. **90**:700 (June 22) 1946.

A case of hepatic osteoporosis with familial cirrhosis of the liver is described. Treatment with a massive dose of vitamin D gave temporary relief from the pain in the legs.

VAN CREVELD, Amsterdam, The Netherlands.

REVERSIBLE FORM OF MEGACOLON. F. L. J. JORDAN, Nederl. tijdschr. v. geneesk. **90**:1292 (Oct. 5) 1946.

In this clinical lecture, the author describes 2 patients with short attacks of fever occurring during the war days. In both cases roentgenographic studies revealed great dilatation of the colon and dolichocolon. With a diet low in cellulose, the attacks of fever and other complaints soon disappeared. The author concludes that in addition to the congenital dilatation of the colon (Hirschsprung's disease) there was present a temporary noncongenital dilatation of the colon. The latter condition is probably the result of an atony, which arises in predisposed patients under the influence of a war-time diet abnormally rich in cellulose. During the attacks of fever, 1 of the 2 patients also had rheumatic complaints and red spots on the skin.

VAN CREVELD, Amsterdam, The Netherlands.

EXPERIMENTAL EPIDEMIC HEPATITIS. J. D. VERLINDE, Nederl. tijdschr. v. geneesk. **90**:1309 (Oct. 5) 1946.

The virus of epidemic hepatitis was observed by means of inoculation of guinea pigs with the blood, urine and feces of patients with the disease. The virus causes specific changes (hyaline necrosis) in the liver of the guinea pig, which could be observed histologically in animals killed ten to twenty days after onset of infection.

VAN CREVELD, Amsterdam, The Netherlands.

Nervous Diseases

STREPTOMYCIN IN THE TREATMENT OF INFLUENZAL MENINGITIS. JOHN R. BIRMINGHAM, ROBERT KAYE and MARGARET H. D. SMITH, J. Pediat. **29**:1 (July) 1946.

Reports are presented of cases of influenzal meningitis in 8 children treated exclusively with streptomycin, both intramuscularly and intrathecally, or with the antibiotic substance in combination with a sulfonamide drug and anti-Hemophilus influenzae type B serum (rabbit). Four patients recovered. Three patients died, and streptomycin therapy for 1 patient was abandoned because of apparent lack of response. In the last mentioned patient development of fastness to the drug was demonstrated. Toxic reactions at the injection site, principally local pain, cutaneous eruptions and augmentation of meningeal signs, occurred but were not serious. The authors conclude that streptomycin is effective against Hemophilus influenzae type B and that its further clinical trial in influenzal meningitis is warranted.

GRULEE JR., Minneapolis.

INFLUENZAL MENINGITIS: REPORT OF THREE CASES TREATED WITH STREPTOMYCIN AND SULFADIAZINE. SYDNEY NUSSBAUM, SOLOMON GOODMAN, CLARENCE ROBINSON and LOUIS RAY, J. Pediat. **29**:14 (July) 1946.

Three infants, 9, 16 and 15 months of age, respectively, with influenzal meningitis were treated with streptomycin both intrathecally and intramuscularly, as well as with sulfadiazine. Streptomycin, 50,000 micrograms, was given intrathecally daily until clinical response was evident; to maintain an antibacterial level in the blood stream, 50,000 micrograms were given intramuscularly every three hours until 3 Gm. had been injected. In the opinion of the authors, the rapid, dramatic improvement in these infants was undoubtedly attributable to the antibiotic substances.

GRULEE JR., Minneapolis.

TRIDIONE, ITS USE IN CONVULSIVE AND RELATED DISORDERS. M. A. PERLSTEIN and M. B. ANDELMAN, J. Pediat. **29**:20 (July) 1946.

The authors present their experience in the use of trimethadione ("tridione" or 3,5,5-trimethyloxazolidine-2,4-dione) in a group of 75 persons, two thirds of whom were between the ages of 5 and 15 years. The disease condition in 50 per cent of the subjects was diagnosed as epilepsy, the number of persons with organic brain disease and the number of those with idiopathic brain diseases being equal. The remainder of the patients had cerebral palsy, dystonia musculorum, behavior disturbances, tetanus, chorea and paralysis agitans. The dose given orally varied from 2.5 grains (0.16 Gm.) twice daily to 10 grains (0.65 Gm.) five times a day (intravenous and intramuscular administration was used in patients with tetanus).

Disappointing results were obtained with the use of the drug for persons with organic epilepsy. Greatest improvement, however, was noted in some patients subject to petit mal attacks. In contrast, trimethadione greatly benefited the majority of those with idiopathic epilepsies, again particularly the group with the petit mal form. In grand mal attacks its value was greatest when used in combination with phenobarbital, but it was not considered an effective primary anticonvulsant. At least a temporarily beneficial effect was noted in the management of behavior disturbances. The authors express the belief that trimethadione exerted a beneficial effect on persons with athetosis but was of little value in those with the spastic and dystonic types of cerebral palsy. Patients with chorea were not benefited. Good results were apparently obtained in the treatment of tetanus in 1 of 2 children in a series of 5 patients. Few side effects were noted, and toxic symptoms, such as visual disturbance or dizziness, occurred in less than 10 per cent of the patients. The authors suggest the site of action of trimethadione may be in the midbrain, the basal nuclei or the cortical connecting tracts of these centers.

GRULEE JR., Minneapolis.

Diseases of the Genitourinary Tract

BILATERAL RENAL AGENESIS. EDITH L. POTTER, J. Pediat. **29**:68 (July) 1946.

Twenty cases of complete renal agenesis discovered in course of 5,000 autopsies on fetuses and newborn infants are reported, together with a review of the literature. Seventeen of the cases were in male infants, and in all patients hypoplasia of the lungs, as well as a characteristic facies, was observed. A comprehensive discussion of probable embryonic aberrations is included.

GRULEE JR., Minneapolis.

THE PATHOGENESIS OF TUBERCULOUS EPIDIDYMITIS. WALTER M. BORTHWICK, Edinburgh M. J. **53**:55 (Feb.) 1946.

The author presented this work as a thesis to the University of Glasgow and received commendation therefor.

Case records for twenty-one years showed 5,476 cases of tuberculosis in male patients, in 402 of which the histories revealed tuberculous involvement of the epididymis. The youngest patient was 8 months of age; the oldest, 63 years. Among the children there were 12 cases in the group up to 5 years of age, 4 in the group from 6 to 10 years of age and 12 in the group from 11 to 15 years of age, or 28 cases of the disease in children in the total of 402 cases. The figures for all ages bear out the evidence that genital tuberculosis in men is commonest in the years of maximal sexual activity. Injury was not of much influence in the production or localization of tuberculosis in these cases; gonococcic epididymitis was seldom, if ever, an influence in the occurrence of tuberculous epididymitis.

This thesis also includes descriptions of the local lesion, coincidental pelvic lesions and associated renal changes, as well as a discussion of the sequence of events in the pathogenesis of tuberculous epididymitis.

NEFF, Kansas City, Mo.

Diseases of the Ductless Glands, Endocrinology

THE EFFECT OF PITUITARY ADRENOTROPIC HORMONE ON THE CHOLESTEROL AND ASCORBIC ACID CONTENT OF THE ADRENAL OF THE RAT AND THE GUINEA PIG. GEORGE SAYERS, MARION A. SAYERS, TSAN-YING LIANG and C. N. H. LONG, Endocrinology **38**:1 (Jan.) 1946.

The injection into rats and guinea pigs of highly purified adrenotropic hormone of the anterior lobe of the pituitary gland is followed by a prompt fall in the ascorbic acid content and a slower fall in the cholesterol content of the adrenal glands. It is suggested that these changes in the ascorbic acid and cholesterol contents of the adrenal gland under the influence of the adrenotropic hormone are associated with the formation and release of the hormones of the adrenal cortex.

JACOBSEN, Buffalo.

THE INFLUENCE OF DIETHYLSTILBESTROL ON ALLOXAN DIABETES PAIRED FEEDING EXPERIMENTS. R. H. JANES and H. DAWSON, Endocrinology **38**:10 (Jan.) 1946.

From the data presented, it is not apparent that diethylstilbestrol U. S. P. is a diabetogenic agent or that it ameliorates diabetic symptoms in the rat.

JACOBSEN, Buffalo.

THE INFLUENCE OF ADRENALECTOMY ON THE UTILIZATION OF ACETONE BODIES. EATON M. MACKAY, ARNE N. WICK and CYRUS BARNUM, Endocrinology **38**:30 (Jan.) 1946.

Adrenalectomy produces an increase in the rate of utilization of acetone bodies in the fasting rat with ketosis. It is suggested that the deficiency in available glucose in this condition is responsible for the increased ketolysis.

JACOBSEN, Buffalo.

ESTROGEN INACTIVATION AND FOLIC ACID. OSCAR KOREF and PAUL ENGEL, Endocrinology **38**:133 (Feb.) 1946.

Folic acid (pteridyl-para-aminobenzoyl glutamic acid) in relatively high amounts inhibits the estrogenic activity of estrone U. S. P. (theelin) to a certain, rather moderate degree. Folic acid, 1 mg. inactivates almost 50 international units of estrone. Folic acid is certainly not the substance responsible for the vigorous estrogen-inactivating potency of liver in vitro.

JACOBSEN, Buffalo.

Diseases of the Muscles, Bones, Joints and Lymph Glands

JUVENILE RHEUMATOID ARTHRITIS: A STUDY OF FIFTY-SIX CASES WITH A NOTE ON SKELETAL CHANGES. JAMES A. COSS JR. and RALPH H. BOOTS, J. Pediat. **29**:143 (Aug.) 1946.

A study was made of 56 patients with juvenile rheumatoid arthritis. This series represents 4.9 per cent of all persons with rheumatoid arthritis seen in the clinic or wards of the Columbia Presbyterian Medical Center. The term "Still's disease" is avoided as it suggests an artificial distinction between arthritis in children and arthritis in adults. In this series, the age at onset of the disease was 12 years or

less. The distribution according to sex of 5 female patients to 1 male patient is the same as in adults. Splenomegaly, hepatomegaly and glandular enlargement may occur at any age.

Eighteen patients (32 per cent) had a family history of arthritis, rheumatic fever or related illness. Thirty-two patients (57 per cent) gave a history of aural or nasal infection or of infection of the respiratory tract preceding or associated with the onset of arthritis. Thirty-nine patients (69 per cent) gave a history of such infections during their illness.

There was anemia in 80 per cent of these patients and leukocytosis (over 25,000 cells) in 17 per cent of them. High leukocyte counts are often associated with a poor prognosis. Hemolytic streptococci were cultured from the throat in 60 per cent of those patients tested.

The differentiation between rheumatic fever and juvenile rheumatoid arthritis is often difficult. The response to salicylates is helpful, as it usually appears more promptly in rheumatic fever. Certain laboratory tests were of little value in distinguishing juvenile arthritis. The titer of antistreptolysin O is significantly elevated just as in rheumatic fever. As in rheumatic fever, there is rarely a positive reaction to the streptococcus agglutination test. Negative reactions do not become positive as the age of the patient increases. Changes in the electrocardiogram occur in both conditions. Myocardial damage or carditis were discovered in seven of the patients in this study on electrocardiograms. On follow-up studies of 6 of these patients, the patterns reverted to normal. Forty-seven per cent of patients showed some cardiac deviation, varying from persistent tachycardia in 13 per cent to the aforementioned electrocardiographic changes.

Twenty-two patients received chrysotherapy; there were 2 instances of moderate toxicity. Gold therapy is no more dangerous in children than in adults.

Certain skeletal changes, cervical fusion, cervical luxation and brachydactylia, which were not previously related to rheumatoid arthritis are described. The characteristic birdlike facies is considered to be the effect of arthritis on the mandible.

Reports on typical patients are presented, including the 2 who died. One of these children was shown to have amyloidosis. Roentgenograms and photographs illustrate the skeletal changes.

FROM THE AUTHORS' SUMMARY.

NONSPECIFIC SPONDYLITIS. H. WISSLER, Helvet. pædiat. acta **1**:451 (Oct.) 1946.

Four cases of nonspecific, subacute or chronic spondylitis in which the diagnosis of tuberculosis was made are presented. In 1 case osteomyelitis of the leg below the knee eleven years previously was the possible cause; in the others the etiologic factor was unknown. The differential diagnosis of this disease from spondylitis tuberculosa is discussed.

FROM THE AUTHOR'S SUMMARY.

Skin Diseases; Allergy

THE TREATMENT OF SCABIES IN CHILDREN WITH A NEW SARCOPTICIDE. T. J. McELHENNEY, J. Pediat. **29**:189 (Aug.) 1946.

A series of 22 cases of scabies treated with an ointment containing "zyclophen" (a mixture of equal parts by weight of 4-chloro-3, 5-dimethylphenyl hydrogen *dl*-camphorate and ortho-phenylphenol) is presented. As result of his clinical observations, the author concludes that an extremely simple, apparently nonirritating and nonpainful agent, surpassing in effectiveness the usual antiscabietic preparations, is available in this sarcopticide. The treatment is described as par-

ticularly effective against the secondary pustular eruptions, and it is capable of bringing about complete and rapid cure through topical application, without complicated adjunctive precautions. The chemical formula of the active ingredient and a prescription for a suitable ointment are included.

GRULEE JR., Minneapolis.

THE TREATMENT OF SOME COMMON DERMATOSES OF INFANCY AND CHILDHOOD. JAMES W. BURKS JR., New Orleans M. & S. J. **99**:1 (July) 1946.

The author stresses the fact that effective treatment of dermatologic conditions in children depends on correct diagnosis. Oily skin can stand frequent watering; ichthyotic skin requires oil; seborrheic skin tolerates frequent bathing. Delicate skins may require colloidal baths or baths with a mixture of equal parts of solution of calcium hydroxide U. S. P. and olive oil.

For edematous erythematous and exudative eruptions, wet dressings are helpful. As the eruption subsides, ointment of calamine or boric acid may be used. For pruritus, menthol and phenol are added to the mixture of solution of calcium hydroxide and olive oil. Sulfur and Peruvian balsam U. S. P. in petrolatum U. S. P. and hydrous wool fat U. S. P. are advised for scabies. Ammoniated mercury U. S. P. leads the author's list for use in treatment of impetigo. In dermatitis venenata he advises application of a 0.5 per cent solution of aluminum acetate and colloidal baths.

For those interested, formulas and details of treatment are given.

BERKELEY, Beverly Hills, Calif.

ACRODYNIA [ERYTHREDEMA POLYNEUROPATHY] PYRIDOXINE. G. FRONTALI, Arch. ital. di pediat. e puericol. **11**:3 (March) 1946.

The author presents a general exposition of the pathogenic and anatomicohistologic aspects of infantile acrodynia (erythredema polyneuropathy). He discusses his series of 10 cases from various points of view—clinical, pharmacodynamic and hemochemical and in relation to the metabolism, the pyridoxine content of the blood and urine, porphyrinuria and the effect on the capillaries of the body surface. A diet devised by the author increases the symptoms, while the administration of pyridoxine is followed by prompt recovery. No similar effect is obtained with the administration of any other known component of the vitamin B complex.

FROM THE AUTHOR'S ABSTRACT.

Surgery and Orthopedics

CONGENITAL DISLOCATION OF THE HIP. BURTON W. TRASK, Am. J. Roentgenol. **55**:299 (March) 1946.

A roentgenogram was made of the skeleton of a newborn infant who had a cutaneous depression at the level of the lumbosacral joint. The joint was reported to be within normal limits. One and one-half years later the patient was examined again and presented a definite dislocation of the right hip. In a review of the original roentgenogram it was shown that the right femur was slightly farther from the pelvis than was the left femur. This case demonstrates that a dislocation can be present in the neonatal period without the presence of all the mechanical factors.

HARRISON, Chicago.

Book Reviews

La vitamina C en los niños de Caracas. By G. Tovar Escobar, M.D. Trabajos del Centro de investigaciones científicas. Publicationes de la Fundacion Biogen, no. 1. Pp. 136. Caracas, Venezuela: Editorial Grafolit, C. A., 1943.

This work is a thesis which was presented by the author in partial fulfilment of the requirements for the degree of Master of Science in medicine at the Central University of Venezuela. It is a comprehensive study of vitamin C in the children of Caracas. The author first discusses the nomenclature of the vitamin—ascorbic acid, cevitamic acid and vitamin C. The chemistry is covered completely, as well as the properties, both physical and chemical. He made a careful study of the amount of ascorbic acid that is required and the effect of massive doses. For instance, he stated that in both men and animals enormous quantities of ascorbic acid, as much as 100 Gm., could be ingested with no serious effect. He observed that vitamin C is not stored to any extent in the body and that taking enormous amounts for a short time is not sufficient for maintenance, but that one must receive small amounts of the vitamin regularly. He found that ammonium chloride or acetylsalicylic acid given with ascorbic acid stimulated the excretion of the vitamin. The author discusses fully the clinical conditions, such as slow healing of wounds, which are caused by an amount of the vitamin inadequate to keep the body in a healthy condition. If the amount of the vitamin is ample, wounds will heal much more quickly, and in most cases in which healing was slow the author detected little vitamin C in the body.

Hemorrhages are more apt to occur where the intake of vitamin C is small. Patients with Addison's disease are made more comfortable if given large amounts of this vitamin. Asthmatic patients who are deficient in vitamin C are greatly relieved by an increased intake and are able to get along with much smaller doses of asthmatic remedies. Dermatitis following large doses of arsenicals is greatly relieved by increasing the supply of ascorbic acid.

The effect of cold storage and freezing on the retention of vitamin C in fruits and vegetables is also fully discussed. Those who store vegetables in the summertime for use during the winter, feeling that they are getting as much vitamin C as they do in the summertime, might well study this work. The loss of the vitamin in the processing and preserving of fruits, vegetables and milk is fully discussed.

The study of capillary resistance which is included gives considerable information. The methods of estimating the capillary resistance are fully discussed. The methods of determining the amount of ascorbic acid in the urine, perspiration and saliva are all evaluated. An interesting investigation was worked out on both men and animals by giving enormous doses of ascorbic acid. On the first day after administration of the dose, the subjects retained a large amount of the vitamin; on the second day a satisfactory amount, and on the third day the amount in the tissues was barely normal. On the fourth day a deficiency began to show; on the fifth day there was a severe deficiency, and on the sixth day, a grave deficiency. In other words, if a person should go six days without any ascorbic acid in his food, he would be in great need of it.

The author studied 63 children in the Municipal Hospital for Babies in Caracas Venezuela. Many of these children were from homes in which the diet was far below par. An exhaustive study of each of the 63 children was made for evidence

of vitamin C deficiency. It was interesting to note, however, that in practically all the children the author found intestinal parasites, in some in large numbers. It must be remembered that in countries without food inspection intestinal parasites are extremely common.

The author's conclusions are as follows:

1. The small number of cases of scurvy among the people of Caracas is not necessarily due to a sufficient amount of vitamin C in the diet, for, according to Kadji and collaborators, many patients show signs of a vitamin C deficiency corresponding to that in cases of scurvy.

2. The mechanism which causes the appearance of clinical symptoms of scurvy in children with extreme vitamin C deficiency has not been determined.

3. In 81 per cent of the children examined who did not seem to be deficient in the vitamin, pronounced deficiencies were observed, leading one to the conclusion that this vitamin plays an important part in the pathologic changes in the deficiency syndromes.

4. In 62 per cent of the children examined, the results obtained indicated extreme vitamin C deficiency, showing that the nutrition among children of the poorer class is inadequate in this nutritional factor.

5. Of the healthy children studied, only 1 was shown to be below normal.

6. Kadji and associates proved that parenteral tolerance is necessary in the determination of vitamin C nutrition in children, but for application in the present situation it is necessary to modify part of the criteria observed by these authors in the interpretation of the results. The modification consists in considering the results of the 8 per cent who show signs of grave deficiency but not clinical scurvy.

7. To avoid vitamin C deficiency in children, it is sufficient to give them orange, lemon or tomato juice after they are 1 or 2 months of age.

8. In all 11 cases studied no relation was observed between the results of Gothlin's capillary resistance test and the vitamin C index.

This investigation is a most complete and exhaustive study of vitamin C, in which every phase of the problem has been covered. Those who are able to read Spanish and who care to learn all that is known about vitamin C can find it in this book. It is not for sale, but may be had by writing the Biogen Foundation, Caracas, Venezuela.

The Rocky Mountain Conference on Infantile Paralysis. Sponsored by the University of Colorado School of Medicine and Hospitals and the National Foundation for Infantile Paralysis, Inc. Price, $1.25. Pp. 199, with 19 figures and 9 photographs. Denver: The University of Colorado School of Medicine and Hospitals, 1946.

The printed report of the Rocky Mountain Conference embodies both the formal opinions, as expressed in papers, and the informal utterances of a galaxy of distinguished workers in the field of anterior poliomyelitis, such as A. B. Sabin, D. M. Horstmann, A. B. Baker and many others. Emphasis is placed on discussions of the unsolved problems in this disease, with the presentation of data and descriptions of several investigative approaches. "Problems in the Field of Virus Infections," including a discussion of latency, are dealt with in a section by Dr. K. F. Meyer.

All phases of practical management and appraisal of the patient with poliomyelitis are covered, including epidemiologic factors, laboratory diagnosis, clinical signs and symptoms, psychiatric reactions, special problems presented by patients with the bulbar type of the disease and all aspects of treatment, from therapeutic procedures in the acute stages of the disease to brief discussions of the use of braces, reconstructive orthopedic technics and rehabilitation of patients left with residual disorders.

The recorded discussions of the papers presented are particularly meaty. In summary, the wealth of material included in this paper-bound volume, though showing evidences of hasty compilation, such as numerous typographic errors, deserves the careful attention of persons and groups who are working, or who may be called on to work, with anterior poliomyelitis.

Bone Dystrophies: A Systematic Review and Correlation. By F. Y. Khoo. Price not given. Pp. 167, with no illustrations. Chengtu: The Canadian Mission Press, 1945.

This monograph presents a rather complete review of the literature pertaining to dystrophies of bone. As a practical manual for study, however, it lacks coherence and would be of little value to the student or practitioner. The basic context consists largely of direct quotations from various authors. The multiplicity of quotations, with insufficient correlation or discussion, is confusing. The monograph is further handicapped by numerous typographic errors and the lack of illustrations. A few interesting charts have been devised by the author to aid in classification of the diseases. Roentgenographic illustrations would greatly enhance the value of an article covering so complicated a subject.

This publication will be of value primarily for the abstracts of the literature it contains.

Plans for an Institution for the Treatment of Emotionally Disturbed Children. Price not given. Pp. 52, with 2 appendixes; no illustrations. Chicago: The Illinois Children's Home and Aid Society, 1946.

The Illinois Children's Home and Aid Society appointed a committee of outstanding pediatricians and psychiatrists to outline a plan for an institution for emotionally disturbed children. This pamphlet describes such a home, with specifications for the building and staff, the latter to cost $81,640 per year. Presumably, copies of the pamphlet may be obtained from the society.

Courage and Devotion Beyond the Call of Duty. Price not given. Pp. 1,024; no illustrations. Evansville, Ind.: Mead Johnson & Company, 1946.

This book, of over 1,000 pages, contains a list of the citations given to medical officers and organizations in World War II. This is the second preliminary edition.

The publisher, Mead Johnson & Company, has done an excellent job in this presentation, and asks for help in the way of corrections and additions. The book is a fit tribute to the men who gave so much for their country.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

Asociacion de Pediatras de Cataluna (Spain)

President: Dr. Emilio Roviralta, Platon, 1, Barcelona.
Secretary: Dr. Francisco Llaurado, Calle Caspe 76, Barcelona.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Dr. W. G. Wyllie, 33 Wimpole St., London W. 1, England.
Secretary: Dr. Philip Rainsford Evans, Keat's House, Guy's Hospital, London S. E. 1, England.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

SOCIEDAD CHILENA DE PEDIATRIA

President: Mr. Cesar Izzo Parodi, Merced 565, Santiago, Chile.
General Secretary: Dr. Jorge Peña Cereceda, Santiago, Chile.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Thursday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Antonio Prado Vértiz, Edison 101, Mexico City, Mexico.
Secretary: Dr. Manuel Mendez, Hospital del Niño Mexico City, Mexico.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenda Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Chicago. Time: June 21-25, 1948.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. John A. Toomey, City Hospital, 3395 Scranton Rd., Cleveland 9.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlantic City, N. J. Time: Nov. 20-23, 1948.
Areal Meetings:
Place: Buffalo, N. Y. Time: April 29-30-May 1-2, 1948.
Place: Milwaukee, Wis. Time: June 28-30, 1948.
Place: Seattle, Wash. Time: Sept. 13-15, 1948.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Grover F. Powers, 789 Howard St., New Haven 4, Conn.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President:: Dr. Alan Ross, 1414 Drummond St., Montreal.
Secretary-Treasurer: Dr. R. L. Denton, 3534 Ontario Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Donovan J. McCune, 3975 Broadway, New York.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.
Place: Seaside Hotel, Atlantic City. Time: May 4-5, 1948.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Leroy T. Stokes, 30 Summer St., Haverhill, Mass.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502-2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Jackson L. Sadler, 109 W. Olive St., Ft. Collins, Colo.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

Alabama Pediatric Society

President: Dr. Ruth Berrey, 2211 Highland Ave., Birmingham 5, Ala.
Secretary-Treasurer: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Place: Birmingham. Time: September 1948.

Arizona Pediatric Society

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truston Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. James R. Boulware, Lakeland.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Honolulu Pediatric Society

President: Dr. Joseph Palma, The Clinic, Honolulu, T. H.
Secretary: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu, T. H.
Place: Various members' homes for combined social and scientific meeting. Time: Third Thursday, 6 p.m., of each month.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Frederick H. Maurer, 331 Fulton St., Peoria 2.
Secretary: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. R. H. McBride, Frances Bldg., Sioux City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Louisiana State Pediatric Society

President: Dr. R. V. Platou, 1430 Tulane Ave., New Orleans 13.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

Medical Society of the State of New York, Pediatric Section

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.
Place: Philadelphia. Time: Oct. 4-7, 1948.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. J. H. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. Harold J. Starr, 803 Medical Arts Bldg., Chattanooga 3.
Secretary-Treasurer: Dr. W. O. Vaughan, 2105 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatrc Society

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. **Time:** 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. **Time:** 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Place: Morrisania City Hospital. **Time:** 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. George E. Brockway Jr., 176 Fenimore St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. **Time:** 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. **Time:** 8:30 p. m., first Monday of each month from September to June

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. H. William Elghammer, 2371 E. 71st St., Chicago.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Shirley Hodges, 2703 Oak Lawn Ave., Dallas, Texas.
Secretary-Treasurer: Frances M. Love, 4585 Belfort, Dallas 4.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Ft. Worth Pediatric Society

President: Dr. Edward M. Wier, 1414 Pennsylvania Ave., Ft. Worth.
Secretary: Dr. James N. Walker, 1812 Tremont St., Ft. Worth 7.
Place: Welch & West Restaurant. Time: 7 p.m., third Friday of each month.

Houston Pediatric Society

President: Dr. George Salmon, 1220 Bartlett St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville–Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Samuel K. Levy, 1694 Nostrand Ave., Brooklyn 26.
Secretary: Dr. Samuel Silber, 865 Park Pl., Brooklyn 16.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New Queens Pediatric Society of Queens, Long Island, N.Y.

President: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N.Y.
Secretary: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N.Y.
Place: Forest Hills Inn, Forest Hills, N. Y. Time: Second Monday of October, December, February, April and June.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Secretary: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. J. B. Snow, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Arthur M. Dannenburg, 235 S. 15th St., Philadelphia 2.
Secretary: Dr. D. Stewart Polk, Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 300 S. Goodman St., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

San Antonio Pediatric Society

President: Dr. Sidney R. Kaliski, 518 Moore Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Variable. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Donald C. Shelby, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.